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THE PHILOSOPHY OF SURGERY*

HARVEY B. STONE, M.D.**

The invitation to give this year's Roy D. McClure memorial lecture is a great honor, and I appreciate it deeply. In attempting to come to grips with this large and somewhat ill-defined topic, certain definitions seem essential. Thus, in rather elementary fashion, surgery may be defined as that branch of therapeutics involving physical interference in the patient's anatomy in the hope that his welfare will be benefited. The general purpose of benefitting the patient's welfare may take two forms: to remove some menacing condition, or to correct or improve some defective or abnormal state of affairs.

The first type of surgery may be spoken of as destructive or ablative surgery. This type is exemplified in a host of specific diseases from acute appendicitis to cancer, and the essential effort is to excise or otherwise eliminate the noxious condition. The imperative restriction is that the measures invoked shall not inflict more damage on the patient than he suffers from the original disorder. The second type, often spoken of as cosmetic, plastic, reconstructive or rehabilitation surgery, seeks not so much to remove harmful diseased tissue as to utilize the patient's existing tissues or other material to overcome disfigurement, deformity, disability, or physiological deficiency. The field is steadily growing in importance. One may cite, for example, the tempting possibility of successful cross-grafting of living tissue for deficiency states and mutilations. The basic problems are fairly simple even though their solution may prove difficult. With great oversimplification they may be stated to be the determination of the extent of the defect or deficiency, the appraisal of the available material for correction and the development of methods for using this material.

Destructive or ablative surgery presents more difficult problems. One must balance the hazard of the existing disease or injury against the danger of its surgical correction, and must realize that many factors involved are ill-defined yet serious. General rules are not always easy of application to specific cases, and many imponderables exist in nearly every case. Therefore, generalizations are not too valuable in discussing the philosophy of this type of surgery. To make a more concrete analysis of the situation it seems best to take one group of conditions in which we now use destructive surgery and show the present status of treatment, unsolved problems, and future possibilities. The subject chosen for such analysis is cancer. One might say that I am attempting to plot the roads ahead in the attack on cancer.

Note that the word "roads" is the plural form, because in the attack on cancer we use multiple forms of therapy. An important aspect of our conception of the philosophy of surgery is the competitive position that it holds in respect to other methods of treatment. Hence, our study must include a brief survey of the more important of these alternative methods which encompass a wide variety of details, but may be grouped roughly into a few categories. These are treatments based on the use

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*The Roy D. McClure Lecture presented May 13, 1958.

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of chemical substances, physical agencies, and possibly biological principles. Chemical substances include groups like the nitrogen mustards, antimetabolites, sex hormones and other steroids, bacterial products, such as Coley's fluid, and radio-active isotopes. The last group could be included in the category of physical agencies — an example of the modern blurring of the distinction between the realms of chemistry and physics, because the most widely used and effective in general of the physical agencies is radiant energy in various forms, one of which is radio-active isotopes. Other and older forms of radiant energy are x-ray, radium, radon, and now perhaps supersonic and infra-red and ultra-violet radiation. Under the general heading of physical agencies must be mentioned also the use of extremes of heat and cold, although the practical utility of these is largely limited to the skin and accessible mucous membranes. The biological reactions, I shall consider in more detail later since at present they consist chiefly of hope and promise rather than of proven practical value. These numerous methods of chemical treatment can be summarized in the words of Stock.[1] "Although no human cancer cures are available, a few steroids, some folic acid analogs, the nitrogen mustards, and related compounds are definitely of use in certain forms of human cancer." A similar summary could be made of the effectiveness of physical agencies, except that longer experience and wider fields of trial have increased the yield of favorable results. However, radiation and other physical agencies give only palliative results in a large majority of instances.[2] All these various methods are destructive of living tissue if employed in excess, and may even be fatal; they are more damaging to neoplastic tissue than to normal structures, but are not highly specific in their effect on neoplastic tissue. The margin between an effective therapeutic dose and a harmful or dangerous one is often quite narrow. In short, we are using what we hope will be a helpful friend not what is always potentially a dangerous enemy.

SURGERY

At the present time surgery is the most widely used and generally successful of all the modalities employed in the treatment of cancer. Surgery may be used for two different purposes, to achieve palliation or to attempt radical cure of the disease. We should distinguish these purposes from each other in our thinking and in our practical work. When there is no hope for a definitive cure it is poor judgment to extend surgical operations beyond what may be necessary to give the maximum of symptomatic relief. For example, a patient with carcinoma of the breast may have proved distant metastases and also a fungating infected local lesion. In such a case simple mastectomy to remove the symptoms of pain, odor, discharge and bleeding is highly desirable, but a radical operation can add no particular increased advantage. Similarly, the clinical symptoms of acute intestinal obstruction due to a malignant growth in the bowel may be completely relieved by either a local resection, a by-passing operation or an enterostomy; whereas, if the disease has spread widely to the liver, lungs or general peritoneal cavity there is no prospect of benefit from more extensive surgical destruction. It is wise to resist the tendency to be confused in this matter and perhaps thoughtlessly to convert a proper and desirable palliative procedure into a semi-radical one.

In the attempt to attain radical cure by operation on malignant disease, there has evolved a general principle that is widely accepted. It may be stated thus: these operations should remove *en bloc* the primary focus of the disease with all the sur-

rounding tissue that can safely be excised, having due care to preserve to the patient his life and the structures necessary for subsequent physiological functions, with freedom from pain and intolerable disfigurement. There will be little quarrel with such a statement but in actual practice rather wide difference in its interpretation has developed. So true is this that it seems highly desirable to discuss in some detail the development of what may be called ultra-radical surgery for treating malignant disease. Before proceeding, however, it is necessary to make a brief appraisal of this classical and time-tried form of therapy which, within limitations, is the best method yet devised for dealing with many forms of malignancy. Not all cases are amenable to radical operative attack. Where the disease involves not a local organ but a general type of tissue, such as the lymphatic glands, surgery of any type has only palliative value. When the patient is first seen with general or distant metastasis, surgery is not a curative method. But in a large group of cases operated upon by the classical types of radical removal, at a favorable stage in the evolution of the disease, recovery with long post-operative freedom from recurrence may be expected. One hesitates to use the term "permanent cure" in relation to malignancy, because of late recurrence even after many years of apparent freedom. However, every surgeon whose work has included wide experience with malignant cases is aware of frequent instances of patients living many years after radical operations and ultimately dying from some unrelated disease without showing evidence of return of the cancer. This is more than can be said of any other form of treatment now available.

Ultra-radical surgery. Progress in fields related to surgery has brought safety of operating and made accessible anatomical areas and organs formerly regarded as too hazardous for attack. Better anaesthesia, pre-and post-operative care, control of infection, wide use of measures such as free blood transfusion, chemical and fluid balance, earlier ambulation, and advanced plastic repair have given a justified freedom of operative attack greatly exceeding that of twenty years ago. With this freedom the surgical treatment of conditions involving the brain and cord, the thoracic structures and the heart and great blood vessels has advanced spectacularly. Eager efforts have been made to apply these new freedoms to the operative therapy of malignancy.

The specific types of operation in question cannot be discussed in detail but they have involved nearly all anatomical regions and major organs. Examples may be cited as hemi-pelvectomy for melanoma of the foot, and removal of large parts of the alimentary tract, half the liver, and spleen, the pancreas, and the omentum for lesions originating in one or other of these organs. Similarly extensive procedures have been employed in the pelvis and about the head and neck. Incidentally these latter are not so new but a revival of much the same thing used and abandoned thirty years ago. These efforts further the first part of the general principle of the surgical treatment of malignancy, namely the widest possible removal of tissues about the primary focus of disease. But one must question seriously how well the second part of the principle is observed by these ultra-radical measures; that is, how much concern is exercised for the preservation to the patient of his life, and if he survives how much possibility is there of reasonable freedom from distress, discomfort, disability and disfigurement. What is being asked is a balancing of the benefits and damages resulting from the newer ultra-radical surgery.

It is well to emphasize again that there is no new principle involved in the ultra-radical operations which remain local excisions albeit greatly enlarged in scope. Hence the same limitations as before apply to using these newer operations in the treatment of system diseases of malignant type like the leukemias, the lymphomata, Hodgkin's disease and others. Also in forms of malignancy, such as melanomata, were spread of the disease frequently occurs by the blood stream, little can be expected in the way of radical cure by any sort of surgical excision. In cases where spread by way of the blood has not yet occurred the usual classic operations should be adequate. If bloodborne metastasis has already taken place no operation offers any real hope of cure. A further limitation of ultra-radical operations is extra requirement of experienced personnel in all the auxiliary services of the operating and recovery rooms, supplies of blood, and specially trained anaesthetists. Most of all is needed the experienced surgeon with courage, judgment, and physical endurance to meet these taxing ordeals with their numerous possibilities of sudden and dangerous crises. Such requirements will restrict for some time the wide-spread utilization of these difficult and hazardous performances.

What reason can be given for the use of such methods? The answer is the belief that a number of cases may be saved and recurrence prevented that would die of cancer treated by the classical operations. This is a potent reason if it can be supported by facts. Herein lies one of the stumbling blocks to a fair and valid appraisal of the merits of these newer operations. Theoretically the addition of a larger area of excision would include some cases in which the disease has not yet extended beyond this larger area but had already transgressed the zone comprised within the limits of the classical radical operations. Not sufficient time has yet elapsed nor a large enough number of such operations been performed to permit any convincing figures to be accumulated. Such figures would need careful scrutiny when available. The known variability in the natural history of malignant disease introduces a factor difficult to judge accurately. Authenticated instances of recurrence of disease have appeared after 10-15-20 years of seeming cure. There are examples of *untreated* cases of carcinoma of the breast, for instance, surviving long periods of years. There is often the question of whether a late appearance of malignant disease after operation is a true recurrence or a second *de novo* cancer. Certain historical facts also bear on this question. Halsted, one of the originators of the classical operation for cancer of the breast, at one time added to it an extension of the area of removal to include the supraclavicular group of lymph nodes. This addition as well as removal of the nodes along the internal mammary vessels and in the mediastinum constitute the ultra-radical form of breast operations sometimes advised with removal of the clavicle. Halsted, who was known as a careful and complete dissector and accurate observer, abandoned the supraclavicular extension because he felt that it added nothing of value to the results of the operation. Bloodgood, Crile, and others, who practiced extensive mutilating operations for malignant growths of the tongue, mouth, jaws and lips, including extensive bilateral removal of the drainage areas of the neck to and beyond the clavicle, abandoned these operations as experience accumulated. One such finding occurred in similar neck dissections, not for cancer but for tuberculosis of the cervical lymph nodes. Frequently after careful and extensive operation, the patient would return in one or two years with multiple enlarged diseased lymph nodes in the very region apparently cleared of all such

structures. In a report of 100 ultra-radical operations of various types Brunschwig[3], one of the earliest proponents of this form of treatment for cancer, was able to report only 12 survivors four years after operation. Who can say there may not have been as good or better results after the classical type of operation.

With consideration for all these known facts, while one still must agree that theoretically the ultra-destructive methods of operating may show additional long term survivors, it appears likely that the number of such survivors will be quite small, perhaps in the range of 2 or 3 percent. The question arises as to whether this salvage, if it really is attained, is worth the price.

These ultra-radical methods entail an additional price for the patient. In the first place, the immediate mortality is greater. It is true that any new surgical operation of considerable magnitude involves the probability of somewhat higher mortality during its developmental stage. But these ultra-destructive operations inherently are more hazardous and still show higher death rates after years of experience. For instance, Brunschwig[3], in the paper published in 1945, reported an operative mortality of 34%. The same surgeon in a second report based on a single type of ultra-radical operation — pelvic exenteration — and covering 315 operations, recorded a rate of mortality for operating room, hospital, and early post-hospital periods of 27%.[4] A comparison of these figures, which may be considered the best available in this field, with those for such classical operations as the Miles abdomino-perineal resection of the rectum and sigmoid, which range from 4% to 7%, shows the price paid for the more destructive methods and outweighs any small increase in the 5 year expectancy among the survivors of the newer type of operations. In the paper by Brunschwig[4] 12 living patients of a group of 104 survivors of operation were followed four to six years, which is less than 4% of the original group.

Increased mortality hazard is not all the price exacted by these methods seeking to raise the long-term survival rate of cancer patients. Among those who survive operation, whether briefly or for several years, there is considerable increase in discomfort, disability, and general invalidism, particular manifestations of which depend upon the anatomical regions involved. Thus patients submitted to total gastrectomy with removal of many adjacent organs may suffer marked loss of weight, anemia, and asthenia. Sometimes after many months of careful and rigorous regimen they may improve somewhat but rarely regain full weight, blood count and vigor. Many remain chronic nutritional invalids. Brunschwig now advises that some small part of the stomach must be preserved to prevent this. Head and neck operations may entail loss of speech, chewing, or swallowing or such disfigurement and consequent subjective distress as make the patient a social recluse. Plastic operations, cosmetic aids and prosthetic devices may ameliorate but rarely conquer these distressing sequelae. The crippling effect of pelvic exenteration with the resulting "wet colostomy" is well konwn. Ingenious secondary operations to relieve this situation have been devised and are still being developed. Sometimes the patient dies of the recurrence of the original malignant disease before these substitute arrangements can receive a fair trial.

Not to be overlooked is the much increased cost in time and money brought about by the ultra-radical operations for those who survive the early post-operative

period. Hospital, nursing and professional care is more prolonged and expensive than is the case following classical radical operations. The result may easily be financial ruin of a family. Even when the patient's resources are sufficient to meet the increased demands, the lengthened period of convalescence and corresponding loss of earning power add another item to the cost of these newer procedures.

The greatly increased area of surgical ablation is too recent to allow final judgment upon its value. The attainment of its objective, the increase in long-term survival of patients suffering from malignant disease, has not as yet been demonstrated. Its disadvantages in increased mortality, morbidity and expense are obvious. Time may show a decrease in these disadvantages and the attainment of the desired objective. I believe this heroic effort to improve our attack upon malignant disease will be disappointing. At the present time, it is undesirable to have wide-spread participation among the profession in the trial of these ultra-destructive operations which are hazardous and costly in the most experienced hands. The limitations to their use described above should be strictly observed. Those who have pioneered this effort, whether it proves rewarding or not, deserve appreciation for courage and enterprise even if one may personally question the soundness of their premises and the practical merits of their judgment. Progress in the study of medicine requires men who will take risks for the testing of new ideas. We also need cool dispassionate appraisal and criticism of such risks. The writer has always been fond of the story of the city in ancient Greece surrounded by three concentric walls. Over the outer gate was an inscription "Be Bold", over the middle gate another "Be yet more Bold", and over the inner gate the admonition "Be not too Bold". In economics one learns of the point of diminishing returns. After a mine has reached a certain depth the cost of bringing up more ore is greater than the value of the ore itself. This situation exists at present in all of the methods of treating malignant disease so far discussed. Whether the attack upon the disease is executed by means of chemical substances, radiation, or surgery the normal tissues also suffer. There comes a point beyond which the damage of the method exceeds its benefits. Each of these agencies has value within the limits set by the point of diminishing returns. Classical surgery, in many forms of malignant disease, gives the best results now attainable. Frequently these results may be improved by combining surgery with chemical or radiation methods. At present the road ahead does not seem to lie in the direction of wider extension of the area of surgical excision.

BIOLOGICAL METHODS

All forms of treatment so far discussed are fundamentally alike. They consist of efforts to remove or destroy the disease by external measures also harmful to normal tissue. Another conception of treatment is the enhancement of the patient's powers of resistance. One may envisage the patient's situation as a struggle between the invasive and destructive powers of parasitic tumor growth and the defensive resistance forces of normal tissues, with the possibility that there may be ways to assist the defense rather than to center all efforts on direct destruction of the invader. That natural defenses do exist is indicated by well-known clinical facts. In rare instances an apparently hopelessly advanced malignant lesion will regress and disappear after or coincident with severe infection. Also, years after the surgical removal of the original cancer distant metastases may appear. Something must have restrained the process.

Then there are rare cases, such as breast tumors, that without treatment slowly grow, become static, regress and finally disappear. Also, many believe that the beneficial effect of x-ray treatment may not consist entirely of its destructive action on the lesion, but in changing the surrounding structures so that they become less favorable for the survival and spread of the malignant growth. Another example of the relation between the progress of the disease and the condition of the host is the reaction of certain types of tumor to changes in the hormones of the patient. Cancer of the breast and of the prostate often show evidence of delayed growth or regression, when the sex hormones are changed by castration or by administration of drugs. These changes are not always predictable and are sometimes confusing and rather contradictory, but do indicate the effect of the host environment upon the growth of the disease. In recent years there has been great interest in the use of this fact in the treatment of these special forms of cancer.

There is evidence from the experimental laboratories that at least some forms of malignant disease in animals are related to micro-organisms of virus type. The chicken sarcoma, the rabbit papilloma, and the milk-factor in mouse mammary carcinoma are examples. It is not suggested that all malignant disease in human beings is the result of virus infection. No factual evidence for such an assumption exists at the present time. But should it develop that any human malignancies are related to virus-like causes, then the type of treatment would seem to be the development of specific resistance on the part of the host, as is now the case in known virus-caused ailments. These considerations support the suggestion that more attention should be directed toward the possible build-up of specific resistance to malignant disease. The writer and his associates have been engaged for the past nine years in a modest and so far not too promising effort to test the practical possibilities of this idea.[5,6]

Whether or not this particular effort to stimulate resistance to malignant disease proves of value, the most promising field for future development is in the direction of increasing or creating specific biological resistance by the host to the disease process. All other forms of treatment depend upon the use of destructive methods, in the hope that the tumor will suffer more damage than the normal tissues, and that the differential damage may destroy the tumor but not the patient. This is not a satisfying principle to depend upon. Classic radical surgery may yield as much as a fifty percent five-year survival rate in certain favorable types of tumor. Also, a combination of radical surgery, x-ray treatment, and hormonal manipulation gives somewhat better results in cancer of the breast than any of those methods used singly. Noteworthy palliative effects may be attained in suitable diseases by some of the chemical agents. All this means we have made considerable progress in palliation, and some progress in apparent cures in certain cases. We still lack a sound basic principle of attack that will pin-point its effects on the malignant tissue specifically and not carry at the same time a serous threat to normal structures and to the patient's general health. Further investigation of biological reactions may reval *the road to success in the attack on cancer.*

At present, many investigators are actively engaged in studying various biological aspects of tumor growth. From such work there may develop the success we all hope for.

SUMMARY

An analysis of surgical thinking in its attack upon one specific type of clinical problem is presented. In this way surgical philosophy develops. In the cancer problem we conclude that surgery is the best currently available form of therapy, but lacks specific accuracy in its effectiveness on the morbid condition. We must hope for some form of treatment that will single out the malignant tissue and destroy it without harm to normal structures. However ablative or destructive surgery employed for other types of illness may be highly specific and leave no need for further improvement; for example, the prompt removal of an acutely inflamed appendix. Here the target is clear-cut and the shot hits the bull's eye. Also, the restrictions and limitations existing in the ablative surgery of cancer do not exist in the field of reconstructive surgery where a completely different set of factors needs consideration. The philosophy of surgery is not some abstract theorizing, but a system of analysing specific problems, discovering specific plans of treatment, and carefully appraising the result.

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PHOSPHATE DIABETES
A REVIEW

GEOFFREY FALKSON, M.B. Ch.B* AND BOY FRAME, M.D.*

Phosphate diabetes is the term proposed by Fanconi for the clinical entity otherwise known as vitamin D resistant rickets.[1,2] Most of the information regarding this condition has been gained by the study of individual cases. Its infrequent occurrence has prevented a cumulative experience by any one group. Larger series have been studied for the most part when the disease presented a familial incidence.[3] The most complete clinical studies have been performed by Swoboda,[4] who reports 11 cases, and by Tobler working with Prader and Taillard,[5,6] who report 16 cases. This paper is a review of data obtained from approximately 150 of the more detailed case reports in the world literature and was prompted by the study at this hospital of a patient with severe osteomalacia due to phosphate diabetes.[7]

Since the description of the familial occurrence of tardy rickets by Baagoe[8] and of similar cases resistant to the usual dosage of vitamin D by Jampolis and Londe,[9] interest has been stimulated in rickets and osteomalacia not complicated by demonstrable renal disease or intestinal mal-absorption, yet resistant to average doses of vitamin D. In 1937, Albright demonstrated in phosphate diabetes the ability of vitamin D in massive doses to overcome what he referred to as an intrinsic resistance to vitamin D.[10] It soon became apparent that despite the clinical remission achieved with massive vitamin D therapy, the fasting serum inorganic phosphorus level remained depressed in many instances, suggesting that the disease was not due to vitamin D resistance alone. Robinson, Harris and McCune postulated that primary renal hyperphosphaturia, as demonstrated by the decreased tubular reabsorption of phosphorus, may explain the pathogenesis of the disorder.[11] This concept was opposed to Albright's stand that the hypophosphatemia in phosphate diabetes resulted at least in part from secondary hyperparathyroidism.[10,12] Either concept may account for the reduced tubular reabsorption of phosphorus and depressed serum inorganic phosphorus found in phosphate diabetes.

Fanconi defined phosphate diabetes as including all cases of osteomalacia without other renal lesions or intestinal mal-absorption and having the following characteristics:[2] 1. Familial, usually with a dominant genetic pattern. 2. Chronic absolute vitamin D resistant hypophosphatemia. 3. Elevated alkaline phosphatase before vitamin D therapy. 4. Normal or hyperphosphaturia, high phosphate clearance, and only minimal increase in phosphate excretion during the Ellsworth-Howard phosphaturia test. 5. Pronounced hypocalciuria. 6. Appearance after the first year. 7. Retarded growth with a sturdy body configuration.

Dent considers that phosphate diabetes is a unifactoral renal tubular defect leading to hyperphosphaturia and osteomalacia.[13] A multi-factoral tubule defect when present would then result in the more complicated conditions of renal tubulur acidosis and the Fanconi syndrome, which may also be associated with osteomalacia.

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REVIEW OF CASES.

Few cases of phosphate diabetes reported in the literature have been sufficiently investigated to completely fulfill Fanconi's criteria. We have chosen patients for review in whom, as far as can be determined, there was no question concerning the diagnosis of rickets or osteomalacia from a clinical and biochemical standpoint. Cases with steatorrhea or evidence of a more advanced renal tubular abnormality, manifested as renal tubular acidosis or Fanconi's syndrome, were excluded. All cases showed moderate or marked resistance to treatment with vitamin D. In only a few cases was sufficient study of the urinary phosphorus excretion available to determine whether this was above normal. Since, however, there is strong evidence that primary renal hyperphosphaturia is the main pathogenic defect the collected cases have been grouped under the heading, renal phosphate diabetes. We suspect that many if not all the cases of vitamin D resistant rickets reported in the world literature are examples of phosphate diabetes. This may be in error since there is no absolute proof that a common etiology is present in all cases. Of approximately 180 available cases we consider the data adequate in only 150.[1,3-5,7,9-11,13-25,27,28,36,37,50-84] A statistical analysis would have little meaning because of variation in method of reporting the clinical data; therefore many of the conclusions in this report are derived from the study of the individual case reports.

There is a positive family history of the disease in a large number of patients. There are 50 families on record with more than one member affected. Pedersen[3] was the first to draw attention to this clinically significant fact. Mitchell and Mitchell[14] on the basis of a family history involving five generations were able to postulate that the disease is due to a single dominant autosomal gene of variable expressiveness.

The youngest case of phosphate diabetes on record was an infant of 7 months described by Harrison.[15] Since the patient's mother had an inactive form of the disease, its presence in the infant was suspected from birth. The majority of patients with the disease fall between the ages of 1½ and 16 years of age. The oldest patient with active disease at the time of diagnosis was 57 years old, and gross deformities had been present for many years prior to the diagnosis.[16] The incidence of active phosphate diabetes is less in adults, there being on record only 12 patients in whom the disease had its onset after the age 14. Since 60 per cent of the cases were females and 40 per cent males, there appears to be no striking sex predominance.

The clinical picture of phosphate diabetes has been described adequately in many of the individual case reports, especially when it has occurred in childhood. A child's first attempt to walk often calls attention to the disease since gradual convex curving of the thighs or genu valgus may appear early. The gait may be waddling and at times suggestive of that seen in muscular dystrophy. General weakness is sometimes present, but true muscle hypotonia is less common than in classical deficiency rickets. The general condition otherwise may be quite good. When the disease occurs in infancy and childhood, there may be relatively little bone pain and tenderness despite rather severe skeletal deformity. Of unknown significance is the association of phosphate diabetes and a number of seemingly unrelated anomalies. These include albinism,[17] mental deficiency,[18] neurofibromatosis[19] and craniostenosis.[20,21]

The serum chemistry is similar to that found in vitamin D deficiency rickets. The serum calcium is usually normal, but occasionally slightly depressed. Among the cases

reviewed the highest serum calcium was 11.3 and the lowest, 7.5 mgm. per cent.[22,23] The average serum calcium for the cases was 9.8 before and 10.8 mgm. per cent during treatment. Persistent hypophosphatemia, considered one of the hallmarks of the disease, is present in almost all cases. The lowest serum inorganic phosphorus value reported was 0.17 and the highest, 7.2 mgm. per cent.[24,25] The average serum inorganic phosphorus in all cases was 2.5 before and 3.5 mgm. per cent during treatment with vitamin D bordering on toxic levels. Considering the large number of infants and young children in this series, we consider the value of 3.5 mgm. per cent to be lower than normal. The alkaline phosphatase is generally elevated, but there are documented cases in the active phase of the disease with a normal value.[5] In pure phosphate diabetes the serum electrolytes will be normal and the 24 hour urinary calcium depressed.

Increased amounts of glucose and amino-acids will not be present in the urine unless there is a more extensive renal tubular defect. By definition, the term pure phosphate diabetes would no longer apply. Dent, however, using paper chromatography, found an increase in urinary glycine excretion in patients with phosphate diabetes resulting in what he calls the "superglycine" spot.[26]

Since the urinary phosphorus excretion in phosphate diabetes has received attention only in recent years, relatively little data is available in the literature for analysis. Further work is needed to evaluate the various factors that control excretion of phosphorus in the urine, both in terms of quantitative values and in terms of the various phosphorus reabsorption tests. A number of authors have studied this problem in patients with phosphate diabetes.[1,5,7,24,26-36] Increased urinary excretion of phosphorus has been found in a high percentage but not in all patients with the disease. However, considering the low serum inorganic phosphorus, a normal value for urinary phosphorus excretion may indicate in actuality an excessive loss. In some cases of phosphate diabetes, this excretory rate has continued even after fasting when the serum inorganic phosphorus had fallen almost to zero.[19]

Roentgenograms of the reported cases in childhood simulate those of florid deficiency rickets. There is generalized demineralization of bone and unusually prominent bony trabeculae. The metaphyses of the long bones are broad and frayed, while changes in the spine occur less frequently. The lamina dura is intact unless the bone changes are extremely severe.

We have been particularly interested in clinically active phosphate diabetes as manifested in late adolescence and adulthood. Heretofore, the greatest emphasis has been placed on its occurrence in infancy and childhood. It cannot be said with certainty that the adult form is the same disease or has the same pathogenesis as that found in childhood, but many of the features are similar. As far as can be determined, the nature of the underlying bone disease is identical. In infancy and childhood, due to the unclosed epiphyseal discs, the picture is that of rickets, while after closure of the discs adult osteomalacia is the result. In both instances, poorly calcified bone matrix is the basic abnormality. Hypophosphatemia, both before and after treatment usually occurs in adult cases as well as in childhood. When the disease begins in childhood it frequently becomes inactive and stationary as growth ceases, but the bone deformities

and hypophosphatemia remain into adulthood. The alkaline phosphatase in these adult cases is frequently normal.[3] We have not considered such adult cases to have active phosphate diabetes. On the other hand, we have found reports of approximately 11 cases in which the disease had its onset during or after adolescence and which continued in a progressive fashion until treatment was instituted. These are included in Table I. As far as could be determined there was no definite family history of rickets or osteomalacia in any of the cases, in contrast to the high familial incidence of the childhood form of the disease.[3,14] Bone pain, tenderness and moderate muscular weakness, seldom complaints in children with the disease, are prominent features in adult cases. A loss in height of 4-6 inches in adults with the disease is common. The x-ray picture in the adult shows no metaphyseal change but pseudofractures occur often. The latter are rare in the childhood form of the disease.

The treatment of phosphate diabetes is not entirely satisfactory. Untreated children reach adult life with gross bony deformities and are dwarfed. There is recorded only one patient whose disease, having begun in childhood, remained active after growth had ceased.[37] On the other hand, when the onset is in the adult there is more apt to be steady progression. For many years treatment has consisted of massive doses of vitamin D and calcium supplements. Since most of the cases were started on very large doses of the vitamin as soon as the diagnosis was established, it is impossible to determine the minimal amount necessary to produce improvement. In the cases reviewed, no clinical improvement was achieved on less than 10,000 units of vitamin D daily, while some patients required as much as 1,500,000 units daily.[11] A limiting factor in such therapy has been toxicity to the vitamin, in some cases resulting in intolerable hypercalcemia which occasionally necessitated reduction in dosage to an ineffective level.

The use of added oral phosphorus in the treatment of phosphate diabetes has been emphasized recently. Saville demonstrated increased calcium and phosphorus retention in patients with the disease who were given such treatment.[34] In another recent case report there was striking clinical and radiologic improvement after the addition of 2 to 3 grams of oral phosphorus daily, whereas treatment with large doses of vitamin D and calcium alone during the previous five years had resulted in only minimal improvement.[7] If the hypothesis is correct that phosphate diabetes is at least partly a consequence of negative phosphorus balance due to primary hyperphosphaturia, the use of oral phosphorus supplements seems physiologically sound.

Many patients with phosphate diabetes have been followed in orthopedic clinics for a number of years with the erroneous diagnosis of osteodystrophy and as a result osteotomies were performed to correct the bony defect. If the diagnosis of phosphate diabetes has been correctly established and large doses of vitamin D already initiated, this must be discontinued while the patient is undergoing various orthopedic corrections. Otherwise, immobilization in addition to the high dose of vitamin D, may result in dangerous hypercalcemia and nephrocalcinosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of phosphate diabetes includes a variety of diseases. Other forms of rickets and osteomalacia must be excluded. It differs from classical

deficiency rickets not only in that there is resistant hypophosphatemia, family predisposition, the spontaneous occurrence at any age, and relative vitamin D resistance, but also in that continued intensive therapy is necessary without assurance of cure. Mal-absorption syndromes with resulting osteomalacia should be differentiated by appropriate studies. Hypophosphatasia, a recently described syndrome simulating rickets from the radiologic and pathologic aspect, is identified by the markedly depressed serum and tissue alkaline phosphatase.[38] The more extensive renal tubular defects with associated osteomalacia, such as tubular acidosis and the Fanconi syndrome, may be differentiated by the presence of systemic acidosis in the former and amino-aciduria as well as glucosuria in the latter. In actuality, the hyperphosphaturia in Fanconi's syndrome might also be labeled phosphate diabetes, but there are sufficient additional features to keep this entity separate from pure phosphate diabetes. Little difficulty is encountered in differentiating hyperparathyroidism and osteoporosis. The hypercalcemia and hypercalciuria in the former and the normal serum phosphorus in the latter are usually sufficient.

Dwarfism and deformed extremities in phosphate diabetes have often resulted in a diagnosis of osteodystrophy or chondrodystrophy. However, in these diseases the serum calcium, phosphorus and phosphatase, are almost always normal and there is no evidence of hyperphosphaturia. There are a number of non-rachitic varieties of crural varus and valgus that have in the past been confused with the bony deformities of phosphate diabetes. Many of these latter patients have had one or more osteotomies for correction of the deformities without recognition of the underlying metabolic defect. When Pedersen[3] reviewed such cases in his clinic, a surprising number of patients with phosphate diabetes were uncovered.

PATHOGENESIS

The pathogenesis of phosphate diabetes is still to be completely elucidated. For many years the resistance of the disease to the usual doses of vitamin D led to the term vitamin D resistant rickets or osteomalacia. This term was strengthened by the fact that many patients so diagnosed responded to vitamin D only in doses bordering on toxic levels. There are several features which indicate that simple resistance to the vitamin is not the most likely explanation for the condition.

One of the strongest arguments that more than a vitamin resistance is involved is the repeated observation that the vitamin D required for improvement in phosphate diabetes calls forth a different set of responses from those occuring during the treatment of deficiency osteomalacia. With a therapeutic response in the latter, one of the early changes is a prompt elevation of the fasting serum inorganic phosphorus. This is due to increased absorption of phosphorus from the intestine as well as to its improved renal tubular reabsorption. This elevation of serum inorganic phosphorus aids prompt ossification of poorly mineralized bone matrix. Enhanced absorption of calcium is an additional factor in the accelerated ossification. It is true that excessive doses of vitamin D used in the treatment of phosphate diabetes will also improve intestinal absorption of calcium and phosphorus. In this instance, however, a low serum inorganic phosphorus often persists despite the fact that radiologic studies may show healing of the osteomalacia. The fact that vitamin D returns the serum inorganic

phosphorus to normal in simple vitamin deficiency osteomalacia, but only infrequently in phosphate diabetes with osteomalacia, suggests a different mechanism of action of the vitamin in the two diseases. In the former its action may be physiological in nature, while in phosphate diabetes a pharmacological action may affect ossification of bone without affecting the internal homeostasis of phosphorus. Further biochemical differences between these two diseases entities are demonstrated by healing properties of dihydrotachysterol in phosphate diabetes, but not in deficiency rickets.[15] If the same biochemical system is at fault in deficiency osteomalacia as in phosphate diabetes (vitamin resistant osteomalacia) these variances in response to vitamin D and dihydrotachysterol are difficult to explain. Despite the fact that in normal individuals excess vitamin D tends to cause demineralization of bone, this action is not seen in phosphate diabetes.[39] This again suggest that the action of vitamin D is not physiological in the latter condition. The relative hyperphosphaturia seen in phosphate diabetes but not in deficiency osteomalacia also points to biochemical dissimilarities.[40] If the two conditions were basically the same disease process, except for the wide dosage difference in response to vitamin D, we suggest that there would not be these striking disparaties either before or after the administration of the vitamin. Contrary to this reasoning, Freeman and Dunsky[22] concluded in 1950 that with massive vitamin D therapy one effect of vitamin D may be accentuated without a second effect being influenced and yet, clinical healing achieved. Harrison's concept of the involvement of two different biochemical systems being affected at the two extremes of dosage is an interesting consideration in this regard.[15] It is also pertinent to ask why a resistance to vitamin D is not apparent in the first few months of life if this is the only etiologic factor in phosphate diabetes. In no case described in the literature has an allergic or hypersensitivity reaction to the vitamin been described which might acount for an acquired resistance.

Since we believe that the disease is not simply due to a resistance to the action of vitamin D, we prefer the term proposed by Fanconi and others of primary renal phosphate diabetes. This implies a relative increased phosphorus excretion in the urine. To demonstrate an absolute increase in urinary phosphorus excretion in the disease is difficult due to the problem of controlling the many factors that regulate its total excretion. However, with the use of renal tubular phosphorus reabsorption tests, renal clearance of phosphorus has been shown to be increased in a number of instances of phosphate diabetes.[1,7,31,32] Winberg and co-workers,[17] on the other hand, associate this high renal phosphorus clearance with an increasing dietary content of phosphorus and propose that these are proportional. Thus they rejected the term phosphate diabetes and continue to prefer the term "primary vitamin D refractory rickets". The proponents of the existence of an increased renal phosphorus clearance in the disease suggest that the main defect is due to either a congenital or an acquired renal tubular defect. Evidence of a primary tubular defect in phosphate diabetes is supported by the fact that there are reported gradations from true phosphate diabetes to the more generally accepted renal tubular defect found in the Fanconi syndrome. The combination of hyperphosphaturia and amino-aciduria, as well as hyperphosphaturia and glucosuria, have been reported in separate cases.[4,5,34] This evidence suggests that the eventual clinical manifestations depend upon the degree of renal tubular dysfunction. It has been suggested that an enzymatic defect in the tubules may be primary in the deficient

reabsorption of phosphorus. A decrease in the alkaline phosphatase staining reaction in the tubules of patients with phosphate diabetes has been reported,[40,41] but not universally.[7] An unusual anatomical configuration of the renal tubules described as a "swan neck configuration",[42] as well as reduced alkaline phosphatase staining reaction has been reported in the closely related but more complicated renal tubular defect decsribed by Fanconi. Availability of renal punch biopsy should make possible further histochemical study in a variety of renal tubular syndromes.

For a number of years Albright has explained the low serum in organic phosphorus in phosphate diabetes partially on the basis of secondary hyperparathyroidism. It is true that in some of the pathological studies of the parathyroid glands in the disease chief cell hyperplasia has been present. There is no definite proof, however, that this hyperplasia represents a hyperfunctioning state. The stimulus for secondary hyperparathyroidism has been considered to be either a high serum phosphorus or a low serum calcium. In phosphate diabetes the former occurs rarely,[67] and the latter is found infrequently. Even in the infant case of Harrison[15] where serum calcium and phosphorus were followed almost from birth there was no exiciting hypocalcemia or hyperphosphatemia that might have acted as an initial stimulus for compensatory hyperparathyroidism. The normo-phosphaturia in deficiency rickets, where secondary hyperparathyroidism is also thought to be in action is in contrast to the frequently seen increased renal clearance of phosphorus in phosphate diabetes. If functioning secondary hyperparathyroidism is in force in both conditions, the hyperphosphaturia only in phosphate diabetes remains unexplained. This evidence favors a primary renal phosphrous loss as the cause for the hyperphosphaturia in phosphate diabetes rather than secondary hyperparathyroidism.

Withdrawal of phosphorus from the skeleton and osteomalacia would be the natural consequence of an abnormal urinary phosphorus loss unless there was replacement from a dietary source. This concept would designate the disease purely as one of disturbed phosphorus metabolism and would relegate the importance of calcium and vitamin D to a lesser role. If phosphorus is withdrawn from the skeleton due to a negative phosphorus balance, mobilization of skeletal calcium would also occur. This does not appear in the urine since the urinary calcium is depressed in most cases. That this mobilized calcium in phospate diabetes may be excreted into the intestines, has received support from the report of Swann.[19] This investigator found on balance studies in patients with the disease that calcium excretion in the stools exceeded the intake.

Since the initial interest in phosphate diabetes many pathogenic mechanisms other than those already discussed have been proposed. In 1932 Cockayne,[9] when commenting on the reported cases of resistant rickets, wondered whether these patients were not suffering from an osseous dystrophy determined genetically rather than from acquired rickets. The idea of a basic defect in osteoid tissue, possibly enzymatic in nature causing difficulty in ossification, has since been commented upon by many other authorities on bone metabolism. An even more generalized disturbance of phosphorus metabolism at the cellular level has found some laboratory support. Sterns and Warweg found the organic acid soluble ester phosphorus of the red blood cells to be increased despite the depressd serum inorganic phosphorus.[43] In one case of phosphate diabetes the serum phospho-lipid fraction was increased twofold.[7] An answer

to the significance of these observations may be found in the more complete analysis of the various phosphorus containing fractions of the serum and red blood cells before and after treatment.

That sub-clinical exposure to toxic agents could cause phosphate diabetes is worthy of consideration. Inhibition of tubular mechanisms is utilized in the action of certain drugs such as benemid and sodium para-aminohippuric acid. Both of these substances have been shown to have as one of their actions the reduced renal tubular reabsorption of phosphorus.[44,45] In lead poisoning and in Wilson's disease hyperphosphaturia has been reported,[46,47] possibly resulting from an inhibition of renal tubular enzyme systems by excessive concentrations of lead and copper respectively. Of even possible greater significance is the production in rats by Harrison of excessive excretion of urinary phosphorus by the injection of maleate.[15] In this instance, glucosuria and amino-aciduria also occurred. The possibility that in phosphate diabetes some unknown toxic substances impairing the renal tubular transport mechanisms of phosphorus and causing hyperphosphaturia has not been excluded. The high family incidence might then be explained on the basis of a common exposure. There is evidence that certain other renal tubular defects such as idiopathic hypercalciuria results from renal tubular damage due to pyelonephritis.[49] There is no evidence to support such a mechanism in phosphate diabetes.

SUMMARY

A clinical review of the disease entity, phosphate diabetes, based on the study of 150 cases gathered from the world literature is presented. The postulate that the entity is due to an intrinsic resistance to vitamin D is critically reviewed. Evidence is discussed that would preferentially designate the condition to result from a primary urinary phosphorus loss, followed in turn by hypophosphatemia and osteomalacia.

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Table 1 — Adult Cases of Phosphate Diabetes

AGE OF ONSET (YRS)	SEX	AGE AT DIAGNOSIS	PRESENTING SYMPTOMS	LOSS OF HT.	PSEUDO FRACTURES	INITIAL (MGM.%) CALCIUM	(MGM.%) PHOS.	ALK. PHOS.	DURING TREATMENT VITAMIN D PER DAY	(MGM.%) Ca	(MGM.%) PHOS.	ALK. PHOS.	COMMENTS
Linder and Vadas.[52] 15	M	19	Pain in tibia. Later in knees and entire skeleton.	+			1.2		Cod Liver Oil	11.0	0.9		Wassermann in CSF positive, in serum negative. Enlarged parathyroids 850 mgm.
McCance.[69] 15	F	20	Rolling gait. Bone pain Weakness.	+		10.5	2.5	23 (N3-13)	500,000 IU	10.8 11.9	4.5 3.9	10.5 Bod. 2.75 Bod.	Parathyroid exploration. Tumor-like degeneration of osteoid tissue moved from right removed from right femur.
Salvesen.[76] 35	F	39	Bone pain. Advancing weakness.	+	+	9.3	1.6	6.68 U.	125,000 IU	8.1	2.5	6.68	Parathyroids macroscopically hypertrophied, microscopically normal.
Salvesen.[76] 54	M	56	Lower back pain. Later in knees and ankles.	+	+	9.9	1.4	2.2 Bod.	210,000 IU 70,000 IU	8.9 10.2	1.8 2.6	3.3	Muscle rigidity.
Smeenk.[16] ?Childhood ? 53	M	57	Lower back pain.	+	+	10.2 9.2	1.8 2.2	25 KA	600,000 IU	10	3.8	10KA	Neurofibromatosis.
Elliott[81] 29	M	33	Stiff back. Later pain and muscular weakness in lower extremities.	+	+	10.6	1.9	11.2 Bod.	500,000 IU	14.2	?4		CSF albumin increased to 220 mgm.%.

Table 1 — continued

AGE OF ONSET	SEX	AGE AT DIAGNOSIS	PRESENTING SYMPTOMS	LOSS OF HT.	PSEUDO FRACTURES	INITIAL (MGM.%) CALCIUM	(MGM.%) PHOS.	ALK. PHOS.	VITAMIN D PER DAY	DURING TREATMENT (MGM.%) Ca	(MGM.%) PHOS.	ALK. PHOS.	COMMENTS
Segar, et al.[36] 20	M	24	Backache after a fall. Later pain R. foot and leg.	+	+	11.0	0.9	8 Bod.	100,000 USP	12.8	2.4		History of syphilis
Nordin & Frazer[37] "Child-hood" (?20)	F	33	Bedridden dwarf.	+	+		1.5 & 0.0		250,000	E			Neurofibromatosis
Dent.[19] 40	F	52	Bone pain.	+	+		Low		1,000,000 IU				Neurofibromatosis
Swann.[19] ?		58		+	+	Norm.	Low						Neurofibromatosis
Henneman.[24] 19	F	33	Pain in feet. Increasing weakness. Later generalized bone pain.	+	+	10.6	0.7	over 25 Bod.	200,000	N	2.4	Low-ered.	(Intermittent minimal glycosuria). Parathyroids showed areas of hyperplasia.
Frame, Smith.[7] 30	F	35	Bone pain first in back and leg.	+	+	11.0	2.0	6.6 Bod.	100,000 USP 180,000 USP	10.0 10.5	2.2 2.6	4 Bod. 5 Bod.	Parathyroidectomy. Showed some areas of Parathyroid hyperplasia.
Lievre, et al.[85] 37	M	41	Back pain. Then lawer limbs in-capacitated.	+	+	9.1	3.1	8.0 Bod.	(Large dose)	9.6	5.6	1.4 Bod.	Neurofibromatosis.

A PREVIOUSLY UNREPORTED EFFECT OF THE PROLONGED ADMINISTRATION OF DESICCATED THYROID

THOMAS BAUMGARTNER, M.D.* AND J. MARTIN MILLER, M.D.*

The effect of prolonged thyroid administration in the euthyroid patient has received a minor degree of attention in the medical literature. Available reports have emphasized the apparent complete recovery of the thyroid gland after abrupt or gradual discontinuance of exogenous thyroid medication administered over varying periods of time.[1-4] Recovery usually occurred within three months after cessation of thyroid feeding, based on both clinical and laboratory evidence. Since the administration of exogenous thyroid hormone suppresses thyrotropic hormone of the anterior pituitary and leads to involution of the thyroid gland, the question may be raised that if a total replacement dose of thyroid were taken over a long period of time, might not irreversible atrophy of the gland eventually take place. We have recently had occasion to observe three patients who had been on thyroid hormone in doses of 120 to 180 milligrams for 15 to 25 years and whose thyroids were refractory to the administration of exogenous TSH at the time they were seen in the clinic. All had been placed on thyroid originally for reasons that seemed unrelated to thyroid hypofunction, and they seemed in no way to differ from the large group of patients whose thyroid therapy is initiated for reasons that are best described charitably as "empirical". One of these cases had been studied in sufficient detail so that certain speculative observations can be made.

CASE REPORT: M. A., a 32-year-old white housewife, was first seen at Henry Ford Hospital in 1942 with the chief complaint of cough. The only symptom possibly relating to disorder of thyroid function was that of fatigue. Physical examination was entirely normal. The blood pressure was 110/70, pulse rate 80. The skin was warm and smooth. The reflexes were recorded as normal. Two years later, she was seen by her family physician for fatigue and nervousness over a family situation. A B.M.R. was performed which, to the patient's recollection, was —30. She was placed on desiccated thyroid up to 180 milligrams daily with no appreciable change in her symptoms. She was again seen at Henry Ford Hospital in the Gynecology Division in 1951, at which time she was taking 90 milligrams of USP thyroid. Her B.M.R. was —17 and a year later, having increased the thyroid dose to 120 milligrams, it was —6. In 1958 her B.M.R. was —14 while she continued on 120 milligrams of thyroid. She was subsequently seen in the Endocrine Clinic where a review of her history revealed that in the previous year she had stopped thyroid for two weeks with no obvious ill effect. The thyroid medication was terminated and six weeks later she noted some cold intolerance, increasing fatigue and had gained ten pounds in weight. The only objective change on physical examination was some slowing of the recovery phase of the deep tendon reflexes. No further medication was given for the next six weeks and on her return she had developed a full-blown picture of myxedema with infraorbital swelling, dryness and thickening of the skin, slowness of speech, constipation, and

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marked slowing of the recovery phase of the deep tendon reflexes. Her B.M.R. was —33. The protein-bound iodine was 1.2 micrograms per cent. The radioactive iodine uptake in three hours was four per cent. In order to ascertain whether the thyroid was capable of being stimulated, five units of TSH were administered daily for three days, at the end of which time the three-hour I-131 uptake was still four per cent. Thyroid was again prescribed. Her most recent B.M.R. was —11 after two months maintenance therapy of 180 milligrams daily.

DISCUSSION: Previous reports on the effects of exogenous thyroid ingestion in euthyroid subjects have emphasized the complete recovery of the thyroid gland after the cessation of treatment. This has been observed in patients receiving physiologic or greater amounts for prolonged periods of time. These reports have stressed the absence of clinical signs of myxedema, even in those patients whose indices of thyroid function did not return to normal or pre-treatment levels for considerable periods of time. The patient of this report presented classical features of myxedema three months after stopping thyroid therapy. The B.M.R. of —33, the P.B.I. of 1.2 micrograms, and the three-hour I-131 uptake of four per cent, all support this diagnosis. The failure of the thyroid gland to respond to three days of TSH administration confirms the presence of primary thyroid failure. Stanley and Astwood[5] have demonstrated that human subjects do not accumulate an appreciable amount of thyroidal radioactive iodine while under the influence of exogenous thyroid hormone, but such glands can be stimulated to normal activity within eight hours following a single small dose of thyrotropic hormone.

We are unable to state with certainty that this patient (or the other two patients referred to in the introduction) did not have hypothyroidism at the time thyroid was first prescribed. Neither can we prove that if they were indeed euthyroid initially, the reason for subsequent hypothyroidism was causally related to the prolonged dormant state of the gland. In our experience, the majority of patients previously given thyroid because of low basal metabolic rates have no true thyroid deficiency. They have not been found hypothyroid by any other parameters of thyroid function, and the responses of the B.M.R. to desiccated thyroid have been highly variable. We consider the patient of the present report to fall into this classification for the following reasons: 1) two years before thyroid therapy, she had no symptoms or findings suggestive of hypothyroidism, and she developed none prior to therapy; 2) the administration of 180 milligrams of desiccated thyroid produced no improvement in the symptoms of alleged thyroid dysfunction; 3) subsequent cessation of thyroid therapy led to frank clinical myxedema, easily recognized by the patient as an entirely new set of symptoms.

These cases were originally studied to see if the long-term administration of thyroid hormone might permanently suppress pituitary thyrotropin with resulting myxedema. Whether or not this happened or spontaneous selective (TSH) failure of anterior pituitary function occurred, we cannot state. If either one, the thyroid gland in addition became unresponsive to exogenous TSH. Other authors have mentioned the importance of withholding thyroid for periods up to six months before assessing the thyroid function after prolonged use of the hormone. We considered this unnecessary because the gland had been found unresponsive to thyroid stimulating hormone.

It is our interpretation that this case represents induced myxedema from prolonged

thyroid feeding in an initially euthyroid individual. This type of therapy will cause suppression of endogenous TSH, leading to involution of the thyroid gland. It may produce eventual irreversible atrophy with inability to respond to thyrotropic hormone, comparable to the state of primary myxedema. This observation is not consistent with previous reports in the literature. In 1941 Farquharson and Squires were the first to call attention to the inhibition of thyroid secretion following continued ingestion of thyroid substances.[1] They gave thyroid to several euthyroid patients with obesity, neuroses, or minor chronic disorders. The period of therapy varied from several months to more than two years. All patients were given at least 120 milligrams of thyroid daily, and for some the dose was 300 milligrams. The treatment was stopped abruptly. The B.M.R. fell rapidly to below pre-treatment levels, and some patients complained of mild fatigue, weakness, and cold intolerance. Over a period of several weeks, however, the B.M.R. gradually returned toward pre-treatment levels. By three months, all had stabilized at the initial level and symptoms previously mentioned had disappeared.

Johnston et al. in 1951 reported further observations with similar clinical conditions.[2] Measurements of the B.M.R., protein-bound iodine and I-131 uptake were made at intervals before, during and after treatment with exogenous thyroid. The dosage ranged from 120 to 600 milligrams of thyroid daily. The period of observation extended from one to three years. Thyroid ingestion was stopped abruptly. The B.M.R. and P.B.I. fell rapidly below pre-treatment levels for one to three weeks, followed by gradual rise to normal levels in two to three months. In the few patients having I-131 studies, the initially suppressed uptakes returned to normal range within four weeks after termination of thyroid feeding. Subjective symptoms of hypothyroidism occurred in some patients, but all symptoms cleared in a short period of time. No mention was made of clinical evidence to suggest myxedema.

In 1951, Greer reported the effect of exogenous thyroid administration on the production of endogenous thyroid hormone by euthyroid subjects.[3] He used the 24-hour I-131 uptake to assess thyroid function. Physiologic amounts of thyroid were given, usually 120 to 180 milligrams daily, for short periods of time. Four of the patients had been taking 180 milligrams daily for several years. Twenty-four hour I-131 uptakes were determined previous to, during and subsequent to ingestion of desiccated thyroid. He found that marked suppression of I-131 uptake could be produced in one week with daily administration of 60 to 180 milligrams of desiccated thyroid in 93 per cent of his 47 patients. One patient required 540 milligrams for several weeks to reduce the I-131 uptake to hypothyroid levels. Abrupt withdrawal of the hormone resulted in a gradual return of the 24-hour I-131 uptake to pre-treatment levels within two weeks. An occasional patient required a longer period to revert to the pre-treatment range. In the four patients on 180 milligrams or more for several years, I-131 uptakes returned to euthyroid range as promptly as those on short-term therapy. No patient developed symptoms or signs of myxedema after stopping treatment. Greer concluded that no permanent injury to the thyroid gland resulted from prolonged exogenous thyroid ingestion in euthyroid subjects.

In 1954, Bartels and Higgins reported four cases in which prolonged thyroid administration was stopped abruptly.[4] All subjects were considered euthyroid when

therapy was instituted, as judged from the patient's history. One patient had taken 240 milligrams of desiccated thyroid daily for eight months. Cessation of treatment caused symptoms suggestive of hypothyroidism, but no clinical evidence supported this. After five months she was euthyroid clinically, and the B.M.R. and serum cholesterol were in the normal range. A second patient had been on 60 mg. of thyroid plus Lugol's solution for 18 months. When these were stopped some symptoms of hypothyroidism resulted but again no clinical evidence supported it. Within four months these symptoms had disappeared and she was considered euthyroid.

SUMMARY: A case is presented of primary myxedema occurring after cessation of prolonged thyroid therapy in what is presumed to have been an initially euthyroid individual. It is felt that long continued use of exogenous thyroid led to permanent atrophy of the thyroid gland. Since the possibility exists that continued use of desiccated thyroid can lead to irreversible damage to this gland, it is suggested that its prolonged use be restricted to those cases in which clinical and laboratory findings indicate a real need for replacement therapy.

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RESULTS OF CERVICAL AND VAGINAL SMEAR EXAMINATIONS AT HENRY FORD HOSPITAL IN 1957

JOHN D. KEYE, JR., M.D.* AND GORDON M. JASEY, M.D.*

A total of 4,361 sets of either cervical or vaginal and cervical smears were examined during 1957. The bulk of the smears were examined by one screener, although on occasion members of the staff and resident staff assisted. A small number of the sets of smears examined represented repeat smears. Smears were repeated at the election of the clinicians, or when requested by the laboratory staff.

METHOD OF REPORTING: The results of the smear examinations were reported as follows:

Unsatisfactory
Negative
Negative (atypical cells; please repeat smears)
Suspicious (please repeat smears)
Positive (please repeat smears prior to biopsy)

Those smears reported as *Unsatisfactory* were deemed so due to paucity of cells, poor staining, or artifacts resulting from air drying or degeneration.

Negative reports were rendered when the screener did not find abnormal cells (other than cells distorted as a result of inflammation or degeneration). These smears were not examined further by the staff.

Occasional cells which could not readily be classified were found. In such instances the report was as follows: *Negative* (atypical cells; please repeat smears). In most instances subsequent smears proved to be negative.

When cells were found having some of the features of malignant cells (usually "dyskaryotic" cells) but lacking clear-cut cytologic evidence of malignancy a report of *Suspicious* was made. Repeat smears were requested. These repeat smears and also occasional biopsy material gave highly variable results. One purpose of this survey was to detect, if possible, some of the causes leading to a diagnosis of *Suspicious*.

A diagnosis of *Positive* was made when screener and staff decided that smears contained cells having cytologic features of malignancy. Repeat smears were requested and biopsy recommended in such cases. In most cases biopsy confirmed the cytologic report of malignancy. As always, there were exceptions.

REASON FOR SURVEY: An effort was made to compare the results of our use of the smear technique with mass surveys in other centers. The results proved to be satisfactory in this regard. Unexpected findings sometimes occurred in subsequent biopsy material. These will be explained. An effort was made to determine the cause of the cells which were *Suspicious*, but not clearly *Positive*.

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TECHNIQUE: Patients' histories, cytologic studies and surgical and autopsy material were correlated when possible. It should be mentioned that almost all of the smears came from the Department of Gynecology and that most of the patients had either symptoms or physical findings which resulted in their being examined by a gynecologist. In such a group of patients a higher incidence of malignancy would be expected than in a "normal" asymptomatic female population.

RESULTS: In considering results of the survey the following will be discussed: age, smear diagnosis, menstrual data, pregnancy, clinical diagnosis, treatment (cervical biopsy, D & C, conization, hysterectomy, x-radiation, and other diagnostic or therapeutic measures), and correlation of smear diagnosis with subsequent tissue diagnosis.

AGE: As indicated in Figure 1, the age distribution curves for patients with Positive and Suspicious smears were similar. Perhaps this is a coincidental observation and is related to the ages of all patients seen in the Department of Gynecology (i.e. most patients being in the 4th, 5th and 6th decades).

Figure 1

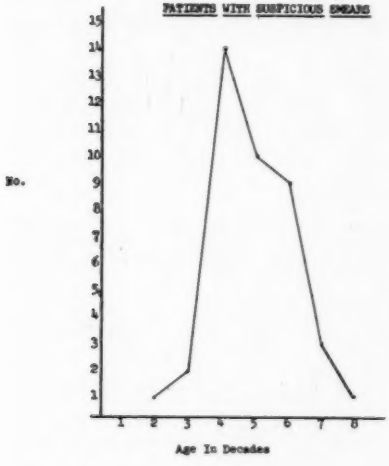
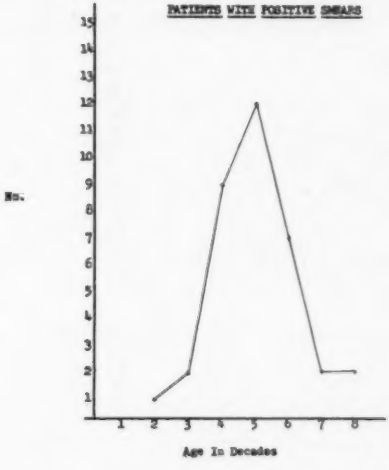


Figure 1 a



CYTOLOGIC DIAGNOSIS: Of 4,361 sets of slides examined 39 patients were reported as *Suspicious* at one time or another. This represents an incidence of 0.9% or 9 cases per 1,000 sets of slides examined.

Of 4,361 sets of slides examined 34 patients were reported as *Positive* at one time or another. This represents an incidence of 0.8% or 8 cases per 1,000 sets of slides.

The actual case finding rate has not been determined because of smears which were repeated and would be higher than indicated by the figures since there are more sets of smears than patients.

MENSTRUAL DATA: Menstrual histories when given were quite variable in patients with *Positive* and *Suspicious* smears. Of the 34 patients with *Positive* smears, 13 were either normally or surgically post-menopausal. Only two of these 13 patients gave histories of post menopausal bleeding. Ten of the 21 patients in the child-bearing age group had varying complaints of menstrual irregularity, the most common being inter-menstrual spotting. Other complaints were of memo-metrorrhagia and one woman noted amenorrhea of 3 months duration. Of the 39 patients who had *Suspicious* but not *Positive,* smears 13 were normally or surgically post-menopausal. Three of these women had post-menopausal bleeding or spotting. Other complaints were of meno-metrorrhagia and one woman noted amenorrhea of 3 months duration.

PREGNANCY: One of the patients was known to be pregnant and one other woman was said to have "possible early pregnancy". In each case the smears were reported as *Suspicious.*

CLINICAL DIAGNOSIS (prior to smear report): Review of the charts revealed clinical diagnoses relating to the gynecologic condition to be infrequently stated prior to the smear report. As a general rule the clinicians described what they saw at time of examination, but did not always state a diagnosis. For this reason it is difficult to state the exact number of "unsuspected" cases of carcinoma which were detected in this survey.

Of 34 patients with Positive smears a clinical diagnosis of carcinoma was made in 6 patients. Diagnoses such as "? carcinoma", "rule out carcinoma", etc. were not counted. Similarly, of the 39 patients having *Suspicious* but not *Positive* smears a clinical diagnosis of carcinoma was made in 4 patients.

TREATMENT: Under treatment are included both diagnostic and therapeutic measures, specifically, cervical biopsy, D & C, conization, hysterectomy, x-radiation, as well as other measures.

Biopsy results are best presented in tabular form (see Figure 2). It is apparent from Figure 2 that 25 patients with either positive or suspicious smears did not have a biopsy at this hospital. In the positive-not-biopsied group, review of the charts indicated that an effort had been made to obtain a tissue diagnosis in all instances. The suspicious-not-biopsied group, however, were usually not biopsied at the election of the gynecologist. It is perhaps relevant in this regard that Figure 2 indicates that 6 of 20 (30%) suspicious-biopsied patients had cervical carcinoma. Biopsy of the remaining 19 patients might well disclose additional unsuspected cancers. It should be stated that 10 of these 19 patients have had negative smear reports since the smear report of suspicious.

It is interesting that of 6 patients with a biopsy diagnosis of carcinoma-in-situ none had evidence of invasive epidermoid carcinoma in the subsequent hysterectomy specimen. Two additional patients with subsequent cervical amputation similarly had no evidence of invasive carcinoma. Residual carcinoma-in-situ was noted in two of the former group and in both of the cases having cervical amputation.

Only one false negative report was made to the best of our knowledge (M. R., H.F.H. No. 889045, C 3855, S58-101). This patient had stress incontinence and "a

Figure 2

BIOPSY RESULTS OF 34 PATIENTS WITH

POSITIVE SMEARS AND 40 PATIENTS WITH SUSPICIOUS SMEARS

CYTOLOGIC DIAGNOSIS	NUMBER OF PATIENTS	NUMBER OF NEGATIVE BIOPSIES	NUMBER NOT BIOPSIED	NUMBER OF PATIENTS WITH: ATYPICAL HYPERPLASIA OF CERVIX	CARCINOMA-IN-SITU OF CERVIX	EPIDERMOID CARCINOMA OF CERVIX, INVASIVE	ADENO-CARCINOMA OF UTERUS
SUSPICIOUS	39	13	19	1	3	3	0
POSITIVE	34	4	6	4*	14≠	4	2**

* 1 Patient had biopsy diagnosis of "Leukoplakia" of cervix.

≠ 1 Patient had biopsy diagnosis of "? Carcinoma-in-situ" of cervix.

** 1 Patient had papillary adenocarcinoma of ovary with secondary involvement of uterus.

small, fine erosion of the cervix which does not appear at all malignant". Subsequent vaginal hysterectomy specimen showed extensive carcinoma-in-situ. The smears were reviewed and, in retrospect, are regarded as *Positive.*

Five cases in the *Suspicious and Positive* group (Figure 2) had a biopsy diagnosis of atypical hyperplasia. This is a particularly interesting group since they present a problem as to disposition. Rawson and Knoblich[1] state that careful follow-up of these patients is indicated since approximately 1/6th will subsequently be shown to have carcinoma of the cervix. In most instances others have obtained an answer by smear and repeat biopsy (conization of cervix) within 2 months.

In regard to the above change and the pregnant state the accumulated reports in the literature suggest that this is merely a fortuitous relationship and that there is no relationship per se between atypical hyperplasia and pregnancy.

One patient with *Suspicious* smears subsequently had a D & C which disclosed tuberculosis of the endometrium. We do not believe there is any relationship between the atypicalities in smears and the endometrial tuberculosis.

In contrast, another patient (P.O., H.F.H. No. 879062, C 1742, S57-5785) with ovarian carcinoma had malignant cells in the cervical smear. The explanation for this was found when the uterus was examined and metastatic papillary tumor could be seen between endometrial glands and projecting into the uterine cavity (Figure 3).

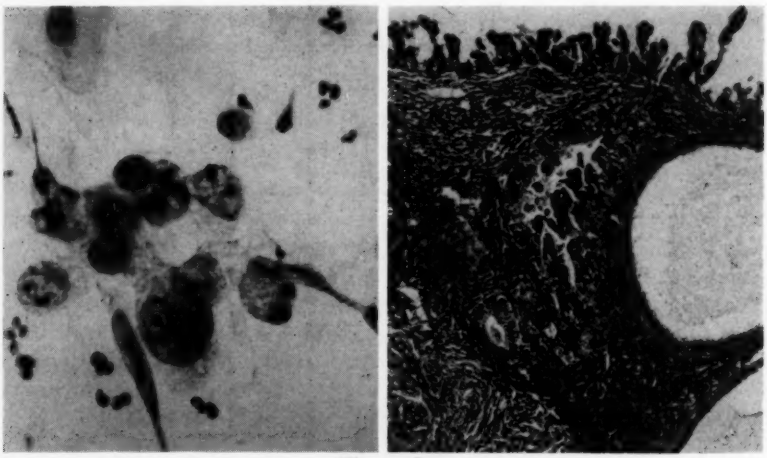


Figure 3

Positive cervical smear (left, x 210) and primary papillary carcinoma of ovary with endometrial metastasis (right, x 170)

SUMMARY:

1. 30% of patients with *Suspicious* cervical smears, who were biopsied, had cervical carcinoma.

2. 85% of patients with *Positive* cervical smears, who were biopsied, had the following pathologic abnormalities:

   64% — cervical carcinoma
   7% — endometrial carcinoma
   14% — atypical hyperplasia

3. 15% of patients with *Positive* cervical smears had negative biopsies.

4. We believe that all patients with *Suspicious* smears should have the benefit of repeat smears or biopsy or both.

5. We recommend that those patients having a biopsy diagnosis of atypical hyperplasia be followed with repeat smears after 2 months and have a conization if these are again *Positive*.

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CHANGES IN BEHAVIOR THROUGH STIMULATION OF THE RETICULAR FORMATION OF THE MONKEY

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R. S. Knighton, M.D.** J. Bebin, M. D.*

This presentation is a sequel to two prior publications[1,2] in which the resulting behavior on stimulating various areas of the reticular formation of the Macaca mulatta was described. Further areas of the reticular formation have been explored by stimulation and the behavioral changes are the basis for this present report.

Technique and Observations: Macro-electrodes, consisting of two #50 stainless steel wires coated with #13 Tygon paint (baked on at 300°F for 30 minutes) were made to adhere together by placing them approximately 0.5 mms. apart, and applying a further coat of Tygon paint (and again baking at 300°F for 30 minutes). The wires were so placed that the tip of one extended 5-6 mms. beyond the other and after the final baking the tips were bared by scraping to expose approximately 1 mm. of each wire tip. The longer wire was bent acutely to form a hook (Figure 1) and to separate the two bared electrode tips by 2-3 mms. The electrodes were placed using the Horsley-Clarke stereotaxic instrument, the hook of the bipolar electrode hooking into the opening at the tip of a #20 lumbar puncture needle shaft which served as a carrier for the electrode into the brain substance (Figure 2). On reaching

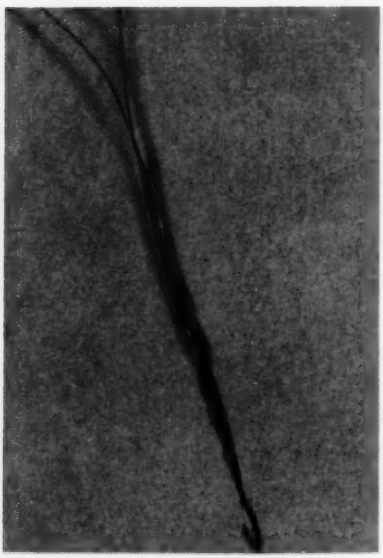

Figure 1
The bipolar "hooked" electrode

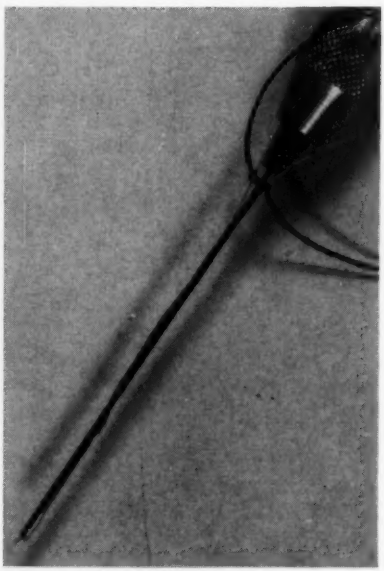

Figure 2
The bipolar "hooked" electrode attached to needle shaft carrier of Horsley-Clarke stereotaxic instrument.

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the intended area in the brain, the lumbar puncture needle shaft was merely withdrawn, the electrode remaining "hooked" in the brain at the intended point.

The two leads of this bipolar electrode were passed through a small nylon button screwed into the animal's skull and securely held within this button by a nylon plug screwed down on the leads through the center of the button — this reduced to a minimum any movement of the electrode within the brain after its placement. The two leads were then led under the scalp to a larger nylon button, also screwed into the skull and having metal jacks fixed into its substance. The leads made contact with these jacks and stimulation or recordings were effected by "hearing aid" type of plugs connected to these jacks and to the Type s4 Grass stimulator or the input of an Offner Transistor type E.E.G. unit.

In earlier experiments macro-electrodes of the Jasper-Delgado type (twisted #50 stainless steel wire coated with plastic paint until rigid enough for placement or wound about a central fine glass core and painted) were utilized.[1]

Prior to electrode placement, the monkeys were brought to a plateau of performance as measured by psychological testing. The oddity test of Harlow[3] was used, the animals having to choose the odd object of three to obtain a food reward. The animals performed consistently for 3-6 weeks at approximately 80 percent efficiency before electrode placements were made. This performance was again checked 48 hours after electrode placement and all animals used in this report were shown to have maintained their pre-electrode placement performance at approximately 80 percent efficiency.

We had previously determined[1,2] that the parameters of stimulation were an important factor in determining the type of response obtained. This applied to other parameters as well as the voltage. The frequency of the stimulating impulse used varied from 350-500/sec., the duration of each train of impulses used varied from 0.10-0.20 msec., and the delay between each train of impulse was 0.01-0.05 msec. These parameters with voltages 0.4-12.0 V (depending on the portion of the reticular formation stimulated) produced stimulations which resulted in little, if any, "Jacksonian like" motor responses. Increasing voltage, decreasing frequency or increasing delay between trains of stimulating impulses resulted in the appearance of the above-mentioned motor responses. Monophasic square top impulses were used in all experiments and the stimulus was continuous throughout the behavioural changes except in the case of post-stimulus hemiballismus to be reported.

In our previous publications[1,2], it was shown that stimulation by bipolar electrodes 2-4 mms. apart placed in a variety of areas of the reticular formation, extending from the anterior hypothalamic nucleus area to the reticular cell mass in the median raphe of the pons produced changes in consciousness that significantly reduced or eliminated the monkey's ability to perform a learned task so that the animal obtained a food reward. In a subsequent publication, changes in behavior were described which resulted from stimulation through more widely separated bipolar electrodes (at least 10-20 mms. apart) with at least one electrode placed within the reticular formation of the monkey.

Stimulation through one electrode in the right subthalamic body and the other in the reticular formation in the contralateral anterior hypothalamus resulted in a

gereralized convulsion followed by approximately 90 minutes of hemiballismic movements of the right arm and leg (Figure 3).

Figure 3
Hemiballismic Responses: Movement of right arm and leg.

Stimulation through one electrode in the nucleus reticularis of the thalamus and the other electrode in the ipsilateral aggregation of cells (reticular formation) at the mesocephalopontine junction produced a "genital response" (priapism and handling of genitals) (Figure 4). Of course, this latter response could have been due to a purely sensory phenomenon through involvement of the medial lemniscus.

Figure 4
Genital response

Since the above investigations, we have made three separate placements of our "hook" bipolar electrode (electrode points seperated 2-3 mms. in the vertical plane).

The first placement was in the region of the head of the right caudate nucleus, the lower electrode being implanted medial to this nucleus in the root of the choroid plexus adjacent to the stria terminalis, and the upper electrode 2 mms above was in the body of the corpus callosum. The inter-electrode resistance in situ was 40,000 ohms (approximately).

On stimulating through this bipolar electrode (monkey #12 using voltages 4.0-5.2, frequencies 400-410/sec., duration of train of impulses 0.20 msec., and delay between

trains of impulses 0.015 msec., a typical yawning occurred 4-5 sec after stimulation commenced. This response occurred with this placement of electrodes on approximately 15 out of 20 trials. Any unusual visual or auditory stimuli appeared to inhibit it and if the animal's foot was touched by the experimenter during the atypical yawn, the monkey flew into a rage. The atypical aspect of the yawn was marked protrusion of the tongue. Immediately after the yawn was completed and with the stimulus continuing, there did not appear to be any significant impairment of the monkey's ability to perform the oddity test.

A second bipolar electrode was placed with the tip in the reticular formation lateral to the red nucleus and dorso-medial to the substantia nigra, and the upper electrode 3 mms. above this region (Figure 5). The inter-electrode resistance was

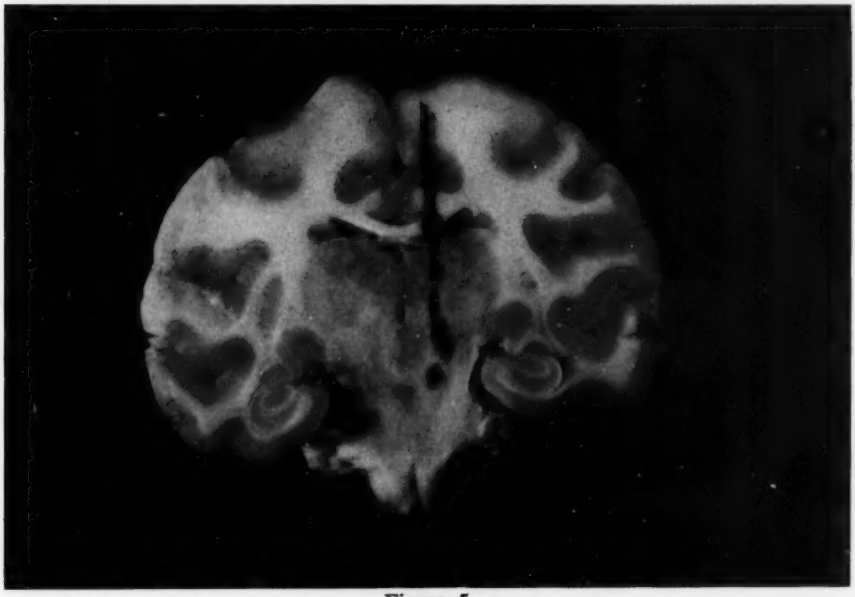

Figure 5

Bipolar electrode in situ in mesencephalic reticular formation (lateral to red nucleus). At the end of the tract is the tip electrode and the upper electrode is situated 3 mms. directly above it.

25,000 ohms. Using voltages 0.60-0.80, frequency of 400/sec., duration of train of impulses 0.1 to 0.2 msec., and delay between trains of impulses 0.010-0.015 msec., yawning occurred 2-3 secs after commencement of stimulation. With this placement it was more difficult to inhibit the yawn by visual or auditory stimuli, and, in spite of such stimuli, yawning would occur by increasing the voltage to 0.90-1.10 V. Some 30-40 yawning responses were obtained and most of them did not show the atypical feature of protrusion of the tongue, (Figure 6). Touching the monkey's foot while yawning brought about a rage reaction, (Figure 7) not as marked as that noted when the yawn was obtained by stimulating through the electrodes in the caudate nucleus and stria terminalis area.

Figure 6
The yawning response.

Figure 7
Rage response.

Following the yawn, continuation of the stimulation did not impair significantly the animal's ability to perform the psychometric test (oddity test). He maintained the pre-stimulus efficiency of 75-85 percent correct choices.

A third bipolar electrode was placed to the left side of the mid-line with the tip resting in the subcallosal region (cerebral fissure medial portion), and the upper electrode approximately 2 mms. above in the corpus callosum. The inter-electrode resistance was 22,000 ohms. Using frequencies of 400/sec., duration of train of impulses 0.10 msec., delay between train of impulses of 0.015 msec., and voltages above 0.80, stimulation produced an adverse motor response with the head and eyes turning to the right, and the right upper limb flexing at the elbow and wrist. This adverse head turning response may be the result of involving the cingulate gyrus in the stimulus field. No yawning response occurred and with voltages below 0.80 no motor response occurred. The animal's ability to perform the oddity test was not impaired significantly (still made correct choice 10 of 12 trials). Ten to twelve separate stimulations confirmed the above observations.

The electrode placements were confirmed 10 days following perfusion of the animal's brain with 10% formalin by examination of gross and miscroscopic sections of the brain.

Discussion: We first observed the yawning response on stimulating with bipolar electrodes placed in the reticular formation just lateral to the red nucleus of a monkey

in 1957[1] (monkey #6). However, this animal was suffering from acute enteritis and died the following day so we were unable to convince ourselves that the morbid state did not contribute to this yawning response. It would now appear this acute enteritis was not a significant contributing factor in view of the many yawning responses obtained on stimulating the same area of a healthy monkey. In this first animal, (monkey #6), sleep followed the yawning, but an increase of 0.20 V in the stimulus awakened the animal, and the monkey would again be made to yawn and fall asleep on reducing the voltage to the previous voltage.

A similar emotional reaction to that obtained on touching the animal, during a yawn produced by electrical stimulation was noted on stimulation by bipolar electrodes (3-4 mms. apart) placed just ventral to red nucleus in 1957[1] (monkey #5). The reaction was brought about by slowly increasing the voltage up to 0.60 V, and if the voltage was increased to 0.90 V extreme panic occurred. French[4] reports panic reactions on stimulating in the mesencephalic reticular formation in monkeys.

The investigations reported in the literature as to the mechanism of yawning are few and provide little, if any, scientific evidence to localize the area of the central nervous system primarily involved in its production. A good review of the literature to 1946 is given by Heusner[5]. Penfield[6] described a case in which lesions involving the third and fourth ventricle produced abnormal yawning and Yakovlev[7] describes yawning as a sign related to disorders involving the basal nuclei. Excessive yawning is frequently seen in cerebellar abscess or tumors[8,9,10,11,12], and its occurrence in an alert patient suggests a search be made for signs of hypothalamic dysfunction. It is interesting that paroxysmal yawning is one of the sequalae of epidemic encephalitis which frequently produces mesencephalic lesions.

One of us (Robert S. Knighton) has observed that while performing a chemopallidolysis (alcohol) the patient frequently yawns on injection of the alcohol into the basal nuclei area. The area of injection is, of course, variable in extent but the injection is directed to the globus pallidus. No doubt, it often involves the ansa lenticularis which has ramifications in the tegmental reticular formation (nucleus mesencephalicus profundus).

Ingram et al[13] have reported contraction of facial muscles on tegmental stimulation of the anaesthetized cat.

It would appear that on stimulating in the reticular formation in the region of the red nucleus, the stimulus is able to bring about the yawn response more consistently and with a shorter period of stimulation than when stimulation took place in the region of the caudate nucleus and stria terminalis. This may be explained by the stimulus having to use a circuitous route to arrive at the more specific centers responsible for the yawning response, and it is interesting to note that the stria terminalis has ramifications in the amygdaloid nucleus and through the hypothalamus to the mesencephalic tegmentum.

The above evidence points to a rather diffuse system that contributes to the yawning phenomenon.

As to the rage reactions that have been noticed on touching the yawning animal (under stimulation): it would appear that the electrical stimulus probable reached hypothalamic centers by descending fibers via stria terminalis or ascending fibers from the mesencephalic reticular formation, to produce an extremely "alert" state so that a slight tactile stimulus could produce the rage or "fight" response noted.

This would offer an explanation as to how stimulation either in the stria terminalis or in the reticular formation of the tegmentum produced a similar rage phenomena. At the present time we are arranging to record electrographically from the amygdala and hypothalamic areas during yawning produced by stimulation of the caudate nucleus and stria terminalis, and by stimulation of the mesencephalic reticular formation.

Summary: Changes in behavior on stimulating the reticular formation in the Macaca mulatta have been described. These include changes in "consciousness", "genital" responses, hemiballismus, rage responses and finally yawning. The yawning may be typical or include the forcible protrusion of the tongue.

The yawning response has been observed in two animals with electrodes placed in the mesencephalic reticular formation or in the region of the caudate nucleus and stria terminalis. A rage response occurred if the animal was touched during this yawn response. A control bipolar electrode placed in the corpus callosum above the mesencephalic reticular formation failed to produce the yawn response or rage reaction on stimulation.

Stimulation of the reticular formation produces a most varied behavior response depending upon the location of the electrode and the area included in the stimulus field. A more thorough investigation of the behavioral responses possible on stimulation of the various areas of this ill-defined system should provide ample scope for extensive research in the future.

This presentation is only intended to show the results of a very gross examination of the possible behavioral changes on stimulating several areas of the reticular formation in the Macaca mulatta.

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PHYSIOLOGICAL TRESPASS IN ANESTHESIA

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Anesthetic practices more than ever are today striving for patient comfort during surgical intervention. The patient expects that comfort will be safely provided, and the surgeon demands that his need for ideal operating conditions will also be met. A poorly conducted anesthesia will obviously impose departures either from safety, comfort or surgical convenience. Physiological processes will be grossly insulted with poor anesthesia. It is perhaps fortunate that the human body will so often recover, in spite of, rather than because of, specific methods of surgery and medicine.

But what of average properly conducted anesthetics — is there serious physiological trespass in this case? In 1938, Beecher[1] of Harvard Medical School suggested that anesthesia is probably akin to sleep; that anesthesia is *not* a grossly abnormal condition; that it is not a state akin to "shock" or "death". Today, however, there is evidence that every time we administer an anesthetic (no matter how trivial the intended surgery is to be) we trespass upon body physiology. We disturb normal homeostasis. Renal function is suppressed, hepatic blood flow is reduced; the cerebral function, especially in the geriatric patient, may be altered for hours and days. Important autonomic reflexes are depressed or dangerously activated. Secreting glands are overly active; the heart's reserve is tested.

One must continually emphasize the "physiological trespass" which occurs even with proper anesthetic administration in order that complacency does not promote another evil — "the trespass of common sense". When anesthetic inductions are hurried as with a "blitz" technique, we frequently obtain severe depression of all physiological processes. We too often accede to the surgical "dream universal" of relaxation as seen only in the fresh corpse. We underventilate in order to provide the quiet "non-pushing" abdomen or to prevent lungs billowing from the open chest. Too often the blood pressure is regarded with a variety of opinions; if low, it helps reduce surgical bleeding. If *too low* (and this is so variable) a vasopressor will often skyrocket the blood pressure to dizzy cerebral hemorrhage levels. If high, we can use more depressant drugs and if *too high,* there are always available a host of antihypertensive drugs. These physiological trespasses, while relative, stem from a breach of common sense.

The poor and the good surgeon have nearly the same mortality rate; but the poor surgeon has a much greater morbidity rate. So too in anesthesia. What should entice everyone training in anesthesia is not the physiological trespass with which we barely avoid trouble but a reduction in the morbidity in the majority group of patients who thrive despite our efforts; and a saving of lives in the minority group who die or survive dependant upon medical or surgical and anesthesiological skills.

Criticism of these evils is being voiced by thinking leaders in "modern"

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anesthesia. Our colleagues across the sea are likewise rousing. The following letter appeared in a recent British journal.

"Sir:

Having retired from anesthetic practice some years ago, I was interested when a surgical colleague invited me to an operation, to see the modern anesthetist at work. The patient was a man of over 80, so far as I could judge from his appearance, reasonably fit. The anaesthetist appeared on the scene with a loaded 20 c. cm. syringe, containing, as he informed me, 1 Gm. Pentothal. This was injected into a vein much quicker than it takes me to describe it. The anaesthetist then disappeared: also, the patient's respirations. I was wondering which would appear first, but the anaesthetist won, with a second syringe, containing, as he explained, 80 mg. Flaxedil. This was injected as quickly as the piston of the syringe could be persuaded to descend. The patient, whose colour had changed through some interesting and picturesque shades of blue into purple and grey, was quickly revived by a few vigorous pumps with the handle of a Mushin absorber and still apnoeic but now pink, was taken into the theatre. Here, cyclopropane was added to the mixture and a diathermy pad applied to a thigh. The anaesthetist must have noticed that I was now getting interested in the other theatre, for he called me back, and was good enough to explain that, as the diathermy machine was at the foot of the table, and we were at the head, "it was quite safe". I was about to protest, when the anaesthetist disappeared again (the patient still apnoeic) but he reappeared a few moments later with yet another syringe, which was injected as quickly as the other two. This, I was told, was 50 mg. of Pentamethonium. Having heard something of the properties of this drug, I felt a little anxious particularly when I could no longer feel the radial pulse. My anxiety must have been apparent for the anaesthetist said: "Why, he's got a beautiful pulse" (that is not how I would have described it, but then, I am not a modern anaesthetist). The anaesthetist again did his disappearing act, to reappear later with a sphygmomanometer, with which he attempted to measure the blood pressure: "That's very satisfactory, the systolic is just below 60". . . . Some 90 minutes later, the surgeon asked me over coffee whether I did not think that was a wonderful anaesthetic. My reply, I am afraid, was couched in such terms as I am sure you, Mr. Editor, would consider unprintable."[2]

This happily is a rarity or a non-entity in this locality. It does highlight the physiological digression possible in anesthesia. It likewise raises a question about the validity of present "balanced anesthesia", a method capable of just the opposite and which often perpetrates insults. Lundy[3] proposed in 1926 that several drugs, each used to a minimal degree, with selection based upon specific requirements would produce less physiolgical trespass. This led to Pentothal for sleep, nitrous oxide for pain relief, curare for relaxation, meperidine to potentiate the nitrous oxide analgesia, a narcotic antagonist to undo the respiratory depressant action of the narcotic and an anticurare drug to undo the effect of the muscle relaxant. The theory is probably excellent. In practice, it can lead to serious physiological trespass. For even with the concomitant use of ventilators, EEG, ECG, and other monitoring devices on every patient, the aberrations seen are probably little different than a single potent agent carried to plane 3 — such as with ether or cyclopropane.

Statistics all too often are an author's own device but do indicate a trend, and as seen in Beecher's[4] well documented report covering ten leading university centers there is a relationship where deaths are related to anesthesia as follows:

One in 880 with ether
One in 1100 with nitrous oxide
One in 1800 with spinal
One in 370 when curare was used.

These data have been criticized sharply and many of us feel the data are misleading, especially where curare is concerned. None the less, we are confronted with several unanswerable questions:

1. Are clinicians correct in relating a higher incidence of cardiac arrests to use of multiple agents?

2. Is it the agent or the skill of the anesthetist? Which is the paramount problem? All the facts are not currently known. One fact we need to know for example is whether a patient is benefited by light anesthesia and the preservation of potent reflexes even though these reflexes may initiate bronchospasm, vasospasm, cardiac arrhythmias, etc. Until an adequate reappraisal is completed, we must consider balanced anesthesia as capable of producing physiological trespass.

TRESPASS TO CIRCULATION

If we administer an anesthetic with a resultant stable blood pressure, some adduce a skillful use of technique and the use of trouble free agents. This often is not so. The ancient Riva Rocci method often does detect deviations. But blood pressure recordings can seldom be taken as often as required to note changes. The anesthetist often is too busy performing an intubation, applying a mask, adjusting an I.V., fastening drapes and carrying out a host of other chores to note these deviations. When the blood pressure is then taken, body homeostasis has often compensated for smaller derangements and a low pressure may have been restored to an artificially "normal" blood pressure. Even if we did employ routine continuous intra-arterial recording, the blood pressure is but a small facet. A pressure can remain relatively constant with:

a) Peripheral resistance constant and slow pulse.

b) Peripheral resistance decreased and increased pulse rate — all dependent on cardiac output; or output can vary and by compensation of heart rate and resistance the pressure can again remain constant. Hence, a "normal" blood pressure is little evidence that a serious trespass upon circulation has not occurred. It is important because we are never certain, when a plunger of a syringe is pushed or flow rate of gas increased, that we might be dealing with a member of that group whose lives depend upon such knowledge. Certain surmizes are possible. The geriatric or pediatric patient, the one debilitated by virtue of weight loss, hepatic, cardiac, renal or cerebral disease, the overly premedicated patient, the one with depleted blood volumes or electrolyte depletion will all be likely candidates for physiological aberrations which approach pathological concern, even when careful anesthesia is obtained. Emphasis is needed that Pentothal produces more than sleep; curare, ether and cyclopropane do more than "relax" and produce sleep with "a whiff". They are also poisons. It says so on the bottle.

TRESPASS TO RESPIRATION

Carbon dioxide early was recommended for resuscitation to promote deeper breathing. More recently some have argued that with normal arterial tensions of carbon dioxide, respiration must be adequate. What has long been suspect, namely, the degree of responsiveness of the respiratory center to a normal stimulus of carbon dioxide is the more important factor. Hence, if the center is depressed, as it always is with pre-anesthetic sedation, inhalation and I.V. anesthetic agents, the center requires a greater stimulus of carbon dioxide for "normal" respiration to occur. If carbon dioxide levels are kept normal, the respiration is depressed under these conditions. If carbon dioxide tensions are permitted to rise this can lead to acidosis. The point is that nearly all our agents for sedation and anesthesia depress the respiratory center. The concensus of opinion is that all anesthetized patients need assistance to respiration. At the opposite end of the scale, some investigators have found that particularly in hypothermic patients with assisted respirations, carbon dioxide may actually be lost and an alkalosis may ensue. The same is said to occur with over-use of ventilators. Whether a fall of the arterial carbon dioxide tensions as we see it is detrimental is not as yet fully understood. Certain it is that this is a trespass of normal respiratory physiology.

DELIBERATE TRESPASS TO CIRCULATION, RESPIRATION AND THERMAL MECHANISMS

With the advent of more radical surgery for congenital defects and for cancer, the surgeon sought help in decreasing blood loss. This was important not only to facilitate surgical dissection but to spare the patient the hazard of repeated transfusions which when in excess of 2500 cc. may be implicated in blood clotting disorders. Since the essential feature of circulation is blood flow rather than just systolic level, it was determined that systolic pressure in most patients could be reduced to 70 mm. Hg. with little difficulty provided blood volume remained stable and vital organs were in dependant positions perfused with blood of high oxygen tensions. While neurosurgeons had previously used arteriotomy for this purpose, it seemed more feasible to lower the perfusion pressure by interruption of autonomic impulses and vasodilatation. Deliberate hypotensive techniques are useful but to a lesser degree than proposed originally since the morbidity and mortality is increased. Little[5], reviewing the first 27,000 cases of deliberate hypotension in the world, found that the death rate was one in 291 and the morbidity rate was one in every 31 cases performed. This was the form of anesthetic technique which caused Gillies[4] first to use the term "physiological trespass".

But we trespass on. Man is a nonhibernating animal. If we lower his temperature, he will assume the temperature of his environment and will not spontaneously rewarm himself as does the woodchuck. Man is most sensitive to changes in excess of 4°F. either side of 98.6°F. Neurosurgeons and cardiovascular surgeons have frequent need to interrupt circulation to vital areas, such as brain, liver, heart etc. for the prevention and control of hemorrhage as well as better direct surgical approach in relatively bloodless fields. Hypothermia is another means of deliberate hypotension. In fact,

both may be combined deliberately and/or co-incidentally. Hypothermia further aids in decreasing tissue oxygen requirements.

When one begins to cool the average adult, shivering occurs and body temperature is raised. So we anesthetize or block autonomic and neuromuscular response. Then the patient will cool. At about 34° to 35° C. if all sources of cooling are removed, in a room at 70° F., his body temperature continues to drop, often to 28-29° C. If rewarming is not done at this time, he continues to cool with eventual death. Rewarming at this point is often a serious problem since with decrease in temperature, the blood pressure falls, the heart rate slows and the blood becomes more viscid. This state prevents rapidity in rewarming. Not infrequently at 30 degrees C., one feels no pulse, hears no blood pressure and respiratory activity ceases. With the help of the EKG, cardiac activity can be monitored; respirations are controlled. This is a physiological response but bordering on a pathological state.

Somewhat germane to this discussion yet not at the wish of the anesthetist is induced (deliberate) cardiac arrest and extracorporeal circulation. Volumes have been written and much is yet to amaze us. The most undefinable but definite changes in tissue oxygen, carbon dioxide, K+, and other electrolytes are enough to cause unexplained deaths in the postoperative period. These later procedures are spectacular and vitally necessary, attendant with much care and deliberation. They are more transgressions than trespass, however.

It may be emphasized that variations of a rather wide range are compatible with life in matters of temperature, cardiac rate, circulatory pressures and respiratory activity. Many patients are even benefited by a selective use of apnea and controlled respirations, the deliberate lowering of blood pressure and rapid autonomic or neuromuscular depression.

These successful accomplishments should not be adopted by us as "routine" or even "physiological" since normal homo sapiens physiologically must remain within very strict confines of temperature, carbon dioxide tension, pH and circulatory performance. Deviations though often successful are physiological trespass.

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THE ZIRCONIUM DEODORANT GRANULOMA: AN ALLERGIC DISORDER*

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Within the last few years, a new and unusual disorder has been described in the dermatologic literature. This disease showed striking uniformity both clinically and histologically[1,2,3,4,5,6], although it was given a variety of names, including axillary granulomas, sarcoid-like eruption of the axillae, granulomatous reaction to deodorant sticks, granulomas of the axillae caused by deodorants, and zirconium granulomas. It was characterized by the presence of persistent painless papules, with minimal acute inflammation and pruritus, appearing in the axillae of persons who had used zirconium-containing deodorants (Figure 1). Histologically, a distinctive granulomatous reaction was seen and was diagnostic (Figure 2). This eruption proved to be virtually refractory to all forms of treatment and its course, following cessation of the deodorant, was one of very gradual, spontaneous involution.

Figure 1

Clinical appearance of axillary zirconium deodorant granulomas.
This patient, a 36-year-old white housewife, developed numerous red-brown papules in the axillae a few months after daily application of a zirconium stick deodorant. Despite cessation of the deodorant the lesions persisted for over two years.

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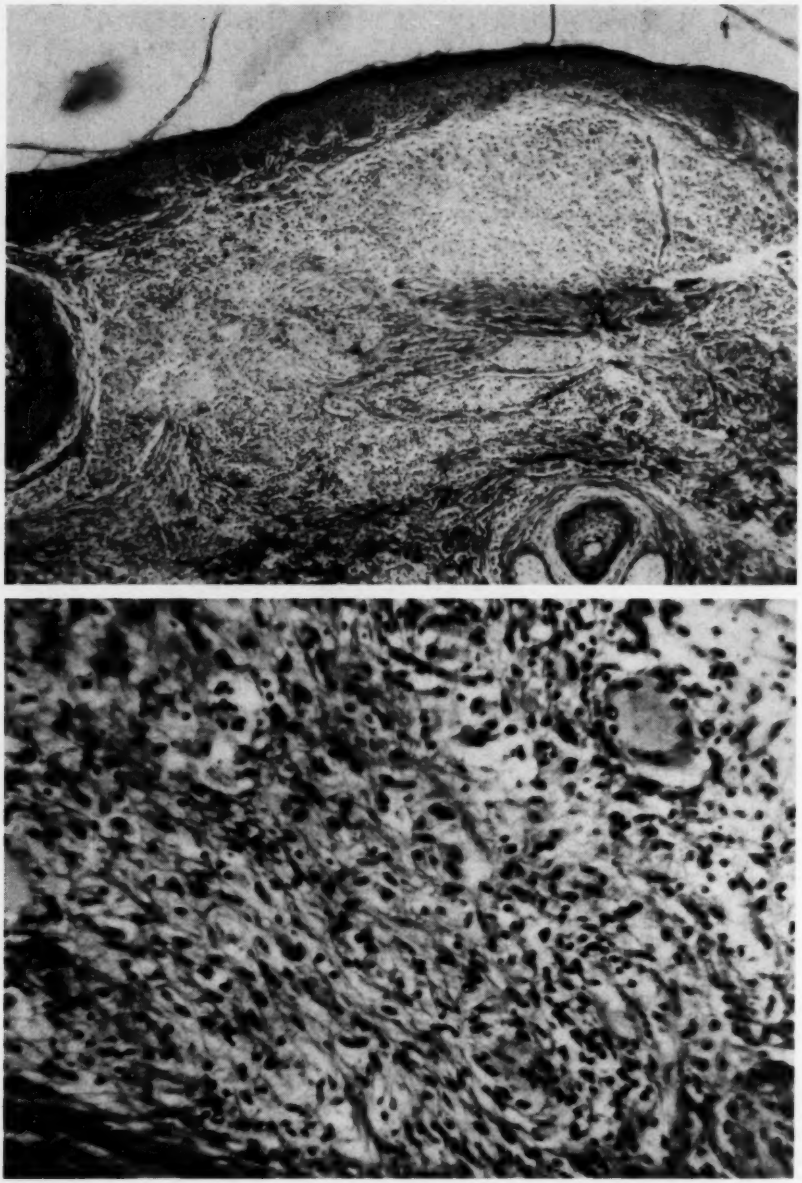

Figure 2

Biopsy of one of the axillary lesions shown in Figure 1 revealed characteristic sarcoid-type of granulomatous patterning. In the upper photograph a low power (x70) microscopic view of the lesion shows nests of epithelioid cells replacing much of the normal dermis. In the lower photograph under higher power (x250) the cytologic appearance of the granulomatous infiltrate is visualized. A giant cell of the so-called Langhan's variety is evident in the upper right hand corner.

Great interest was evinced in this disorder and, in less than two years (1956 to 1958), some 70 cases were described in the literature and a variety of speculations made as to its etiology. Prominent among these were foreign body reactions to zirconium[1,2], to contaminant metals such as beryllium[7] or hafnium[8], to the lipid[9,10], or other inert ingredients of the deodorant vehicle[11], and secondary apocrine sweat extravasation[12] or follicular wall degeneration[13]. However, there was little or no experimental support for any of these possibilities, and neither the incitant or incitants nor the mechanism by which the disease was produced were identified.

In this paper we should like to review our experimental and clinical studies of this distinctive new dermatosis. We have elected to call this new condition the zirconium deodorant granuloma. As a result of these observations, we have concluded that the axillary granulomas that develop incident to the use of zirconium deodorants are the result of a specific allergic hypersensitivity to the metal zirconium which manifests itself as a stable, sarcoid-like granuloma.

The Zirconium Deodorant Stick

It should be emphasized that no single deodorant preparation had been used by all of the patients described in the literature. However, the vast majority had applied a new stick-type deodorant containing sodium zirconium lactate. This stick was essentially a soap-alcohol-gel composed of sodium stearate, ethyl alcohol, carbitol and water with approximately 10% of an aqueous solution of sodium zirconium lactate, and small amounts of hexachlorophene and a perfume incorporated into the basic gel.

Each of the components of this stick alone or in combination was suspect in the production of this granulomatous disorder. However, it was difficult to predict which of these substances was causal. The sodium stearate seemed a quite unlikely candidate since the daily use of soap for years by many milllions of people on broken and unbroken skin has never produced a single granuloma. Similarly the ethyl alcohol, while at times capable of producing transient irritation, has never been known to induce such chronic change despite its ubiquity in cosmetic and topical medicinal products. Carbitol/diethylene glycol mono-ethyl (ether) as a congener of glycerine is miscible with water and extensive studies have indicated that it is essentially non-irritating to rabbit skin[14]. However, absorption of large amounts of carbitol can prove fatal to these animals. Hexachlorophene has been used for many years as a germicide for surgical scrubs. It has also been employed topically in creams and lotions on adult and infant skin without ill effect. The very small quantities of perfume that were present in the stick would seem to make it an unlikely possibility also.

Of all the ingredients of the stick deodorant, zirconium loomed as the most logical canidate for the granulomagenic agent. Indeed, the majority of observers were of the opinion that it was in some way responsible, since the appearance of this new granuloma coincided with the introduction of zirconium in deodorants. Zirconium, a metallic element in group IV period V of the periodic table, is normally found in the earth's crust as an oxide or silicate in a concentration of about 0.22%. It is not radio-active and is closely related to hafnium chemically. Actually, as much as

2% hafnium has been found in the purest zirconium preparations. Sodium zirconium lactate is a recently synthesized salt. It is used as a 40-45% aqueous solution (Ph-7.5-8.2) which is compatible with soap. In the axilla its primary action is as a deodorant and it produces this effect apparently by reducing the surface bacterial flora and probably also by forming a complex with the malodorous fatty acids. Any antiperspirant effect it may achieve is the result of eccrine poral closure in a manner similar to that of the aluminum salts. However, in the axilla this effect is not remarkable.

Zirconium has long been regarded as a very inocuous substance. Careful toxicologic studies support this[15,16,17]. As a metal it has been employed successfully in surgery as bone screws, cranial plates, intramedullary pins, sutures, and bone clips[18]. In animals its introduction in both soluble and insolube forms parenterally, by ingestion and by inhalation for as long as two years has not produced significant acute or chronic change[19,20,21,22]. Granulomas have not been reported in men working with zirconium in industry nor have pulmonary changes been observed. Its use topically (4% zirconium dioxide ointment) in patients with poison ivy dermatitis has not proved harmful[23,24]. Even intravenous administration of zirconium salts has been safely employed in patients with pyodermas[25]. The consensus of opinion was that zirconium in any form seemed to be a safe and essentially harmlesss compound for man. Thus, despite the circumstantial evidence incriminating zirconium as the granulomagenic substance, there was little in the literature to support such suspicion. Moreover, it should be pointed out that the new stick-type vehicle used in these deodorants was of very recent vintage also, and this lent credence to the view that one of the components of this stick or a contaminant was responsible. It thus became apparent that only through careful experimental study could one identify the substance or substances responsible for this new dermatosis.

Experimental Studies

It was stated earlier that as a result of extensive experimental investigation we concluded that the zirconium deodorant granulomas were the result of an allergic hypersensitivity of these patients to the metal zirconium. These studies have been carefully detailed in another report[11]. They were carried out under controlled conditions in healthy adult male volunteers. They may be summarized briefly as follows:

(1) Experimental production of histologically proved axillary granulomas identical with those of clinical cases was achieved in two (subject No. 2 and subject No. 35) of fifty subjects by the daily intensive (5 minutes) application to the axillae of deodorant sticks containing sodium zirconium lactate in both 5 and 10% concentrations. Sticks containing zirconium in 1% concentration produced no such reaction. These granulomas were typically chronic persisting for as long as six months following cessation of the zirconium deodorant sticks. Several other subjects developed transitory acute inflammatory changes to the 5 and 10% zirconium sticks, but these reactions were clearly non-granulomatous histologically. Control sticks, identical except for the absence of zirconium, failed to produce any acute inflammation or granuloma in any of the fifty subjects.

(2) Zirconium deodorant sticks deleted of the hexachlorophene, carbitol, and perfume regularly found in the commercially available sticks, were equally capable of inducing the granulomatous reaction.

(3) Substitution of 5% aluminum chloride for the sodium zirconium lactate in the deodorant sticks failed to result in the development of axillary granulomas.

(4) There was no epidermal (contact) sensitivity to zirconium or any of the other ingredients of the deodorant stick as evidenced by routinely negative patch tests to the deodorant sticks in all of the experimental subjects.

(5) Intradermal injections of dilutions of aqueous solutions of zirconium salts reproduced the granulomatous reaction in the two subjects (No. 2 and No. 35) in whom the axillary granulomas were seen to develop. Injection of these zirconium salts in many normal control subjects and injection of all other ingredients of the deodorant stick, as well as other representative metals (beryllium and silicon) in subjects No. 2 and No. 35, and in the control subjects, failed to produce any such response. Table I depicts the results of these studies.

(6) In a concentration of 1:10,000 aqueous solutions of soluble salts of fifty-seven elements of the periodic table also were injected intradermally in the subjects No. 2 and No. 35, and in the twenty control subjects. In all of the men so treated there were no granulomatous reactions at any of the injection sites except at that of zirconium in subjects No. 35. It is to be recalled that he responded similarly to 1:10,000 zirconium in the previous series of injections (Table I). The elements that were included in this second series of intradermal tests included:

Aluminum	Europium	Manganese	Silicon
Antimony	Fluorine	Mercury	Silver
Arsenic	Gadolinium	Molybdenum	Strontium
Barium	Gallium	Neobium	Tantalum
Beryllium	Germanium	Neodymium	Tellurium
Boron	Hafnium	Nickel	Terbium
Bromine	Holmium	Palladium	Thulium
Cadmium	Indium	Praesodymium	Tin
Cerium	Iodine	Rhenium	Titanium
Cesium	Iridium	Rhodium	Tungsten
Chromium	Lanthanum	Rubidium	Vanadium
Cobalt	Lead	Ruthenium	Ytterbium
Dysprosium	Lithium	Samarium	Yttrium
Erbium	Lutetium	Scandium	Zinc
			Zirconium

These experimental studies indicated that zirconium and zirconium alone was the critical substance responsible for the development of the granulomatous reactions seen in this disorder. Furthermore, the pathogenesis of these granulomas was shown to be the result of a specific hypersensitivity, probably allergic in nature, to the metal zirconium.

Our next step was to confirm these findings in clinical patients with the zirconium deodorant granulomas.

Table I

Intradermal Injections (0.02 cc)	Sodium Zirconium Lactate				Zirconium Chloride		Zirconium Nitrate		Beryllium Sulphate	Colloidal Silica	Other Components of Deodorant Stick*
	1:100	1:1000	1:10,000	1:100,000	1:1000	1:10,000	1:1000	1:10,000	1:1000	1:1000	1:1000
Subject No. 2	+	+	0	0	+	0	+	0	0	0	0
Subject No. 35	+	+	+	0	+	+	+	+	0	0	0
Controls (20)	0	0	0	0	0	0	0	0	0	0	0

*The various ingredients of the stick were injected alone and in combination in the above concentrations. They included sodium stearate, hexachlorophene, ethyl alcohol, carbitol, and perfume.

Clinical Studies

Four patients with zirconium deodorant granulomas were available for study. All had the typical histologically proved granulomatous lesions in the axillae and all were in good health. A battery of general medical studies were within normal limits on all of these patients. These patients were women, ranging in age from 23 to 42 years. Three of the four women had used the zirconium stick deodorant for at least two months prior to the appearance of the eruption. However, one patient states that the lesions appeared after only two applications of the stick. In each case all forms of treatment, including topical steroids, were ineffective. The chronicity of the lesions was an outstanding feature in these patients, and in one patient residual papules were still visible over two years after cessation of the zirconium stick and other deodorant applications.

Special studies performed on these patients included:

(1) Intradermal injection (0.02 cc.) of 1:1000 and 1:10,000 dilutions of aqueous sodium zirconium lactate solution produced a papule in 10 days in three of the four patients. On biopsy these papules showed the characterstic granulomatous picture. The fourth patient responded similarly only to the 1:1000 dilution of the zirconium solution. None of the four patients showed any visible response to 1:100,000 sodium zirconium lactate.

(2) Intradermal injections (0.02 cc.) of 1:1000 beryllium sulfate and 1:1000 silicon dioxide were negative in all four patients. Patch tests to zirconium deodorant stick (full strength) were negative at 72 hours in all four subjects. However, in one subject, a small papule (Figure 3) appeared at about one month. Although involuting

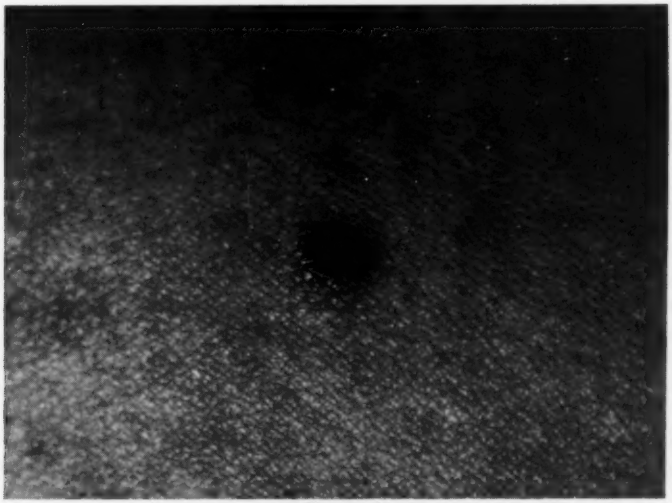

Figure 3

Granulomatous reaction appearing at site of patch test to zirconium stick deodorant. Four to five weeks after a negative response (72 hours) to a closed patch test to a standard zirconium stick deodorant, a papule (shown above) appeared in the patch test site in one of our clinical patients. Histologically this papule showed granulomatous change comparable to that seen in the axillary granulomas.

gradually, it was still evident six months later. This lesion was similar clinically to the axillary granulomas and proved to be granulomatous histologically also.

Discussion

The metals, silicon and beryllium, have long been known to be capable of inducing cutaneous granulomas in some individuals after accidental inoculation[27,28]. In order to determine the presence or absence of these metals as contaminants, we had spectrographic analyses performed on the commercial sodium zirconium lactate solution used in our studies. Many elements were tested for and several were found to be present, in addition to the major constituent, zirconium. Silicon was detected in a concentration of about 0.008%, but beryllium was not found. All of the other elements found were in similarly low concentration and included aluminum, boron, calcium, chromium, iron, magnesium, nickel, and strontium. These were included in the test series of injections made on the experimental subjects, it should be recalled, and were found to be incapable of eliciting a granulomatous reaction.

Although a perusal of these studies leaves little doubt that these patients manifested a hypersensitivity to zirconium, that this hypersensitivity was allergic in nature requires further amplification.

Allergic states are *acquired,* not inherited. Although we have no skin tests or other information indicating the lack of allergic hypersensitivity of these individuals prior to their exposure to the zirconium deodorant sticks, we may presume that they had no such prior hypersensitivity. This hypersensitivity developed some time during the period of application of the deodorant sticks. More compelling evidence that this zirconium hypersensitivity is acquired is available in another experimental subject (not recorded here and not a part of these studies) in whom initially negative intradermal injections of zirconium became granulomatous several months later. Careful study of this subject verified the specific hypersensitivity to zirconium.

Allergic states are *specific.* The specificity of the reactivity of these subjects to zirconium should be apparent after a review of the data outlined above. Moreover, the ability to respond to great *dilutions* of the zirconium points to the allergic nature of this *unusual* reaction.

Demonstration of an antigen-antibody reaction is an important and ultimately requisite step in the confirmation of allergic reactions. We are studying this problem at the moment. Classical serological tests and serum passive transfer techniques for the demonstration of antibody have not been of value possibly because the antibody concerned with this form of allergy may well be cellular. Modified cell transfer methods and other in vivo and in vitro methods are being employed at present.

The failure to identify the antibody concerned with the hypersensitivity reaction to zirconium in the cases described herein does not invalidate our thesis that this reaction is truly allergic in nature. It should be recalled that other forms of allergy were well accepted as such many years before any antibody was ever demonstrated. Tuberculin allergy and contact allergy are excellent examples in point. It is only within recent years by means of specialized cell transfer techniques that these forms of allergy have realized antibody demonstration.

In the axillary zirconium deodorant granulomas which are seen clinically, the possible route or routes of entry of the zirconium have caused much discussion. In women, in whom this disease has occurred predominantly, shaving of the axillary hair is such a common practice that it was regarded as an important factor in the development of this dermatosis. Indeed, in one of our experimental subjects in whom we produced the deodorant granulomas, the lesions could be clearly seen to develop in a linear shaving cut. However, they have also been observed beneath focal areas of miliaria. Actual streaming of microparticulate material through the miliarial vesicles and down into the dermis could be observed histologically. It is our feeling that any process, dermatitic or traumatic, which destroys the integrity of the epidermis or its impermeable barrier will allow for ready absorption of the essential granulomagenic substance, zirconium. Actually, in these hypersensitive individuals, it is likely that enough zirconium is absorbed through the major normal route of absorption, the pilosebaceous apparatus.

Further consideration of the natural history of the zirconium deodorant granuloma as it relates to the allergic process is in order. The affected patients almost uniformly give a history of having used a zirconium-containing product for weeks to months prior to the appearance of their papular eruption. This, then, is the period in which the patients are non-allergic and will not react in this fashion to zirconium. In the latter part of this period they become sensitized to the zirconium. Once this sensitivity arises, residual or additional zirconium in the skin results in a delayed allergic granuloma formation. This latter phase, the development of the granuloma following exposure to the zirconium in the sensitized individuals, represents the *reaction time*. For this form of allergy the reaction time is about two to three weeks for the development of a mature, fully-formed granuloma, although in more sensitive individuals, it may be shorter. In a few patients, the granulomatous reaction developed after what was believed to be the initial contact with zirconium. In these instances, which must be quite uncommon, we can assume that the patient had had prior exposure to zirconium, possibly as an inhalant, with prior sensitization. The concentration of zirconium in the deodorant sticks which will elicit the granulomatous response after topical application was shown to be 4% or above. However, it is possible that in more sensitive subjects one might expect even trace amounts of zirconium in any deodorant or other topical preparation to produce this response. We have no evidence as to the critical concentration necessary to induce sensitization to zirconium, but would feel that as with other forms of allergy, higher concentrations would more readily produce this effect.

Treatment of the zirconium deodorant granuloma has been generally disappointing. Systemic steroid therapy may produce temporary improvement and local injection of hydrocortisone may induce resolution of the lesions. This is quite in keeping with the allergic nature of the disorder. Topical treatment is ineffective in reducing or clearing the basic granulomatous process and is usually unnecessary for the management of any secondary acute inflammatory changes or pruritus since the latter are not prominent features of the condition. Cessation of zirconium deodorants and avoidance of all zirconium-containing products is necessary, of course, and eventually within 1-3 years the granulomatous lesions will involute spontaneously. It is quite probable that this clinical entity, the zirconium deodorant granuloma, will rarely be seen in the future

since zirconium has been removed from the market as a deodorant. However, individuals who have developed such sensitivity should be advised to avoid further contact with zirconium. This allergic sensitivity is not localized to any area of the skin nor to the skin alone. It is generalized in nature and it is conceivable that a granulomatous "zirconiosis" of the lungs could ensue after inhalation of the element in industry or accidentally in dust in a given area of the country. Furthermore, it would seem judicious to re-examine the use of zirconium in surgical plates, intramedullary pins, sutures and the like in certain patients.

In an earlier part of our study we learned that a granuloma develops when appreciable quantities of sodium stearate were introduced into the dermis. Initially we were convinced that this substance was responsible for the deodorant stick granulomas. However, we later came to realize that this was not the case, and that sodium stearate was producing a simple, non-allergic granuloma of the foreign-body type. In another paper we have recorded our findings with this non-allergic granuloma[29]. Sodium stearate is not responsible for the clinical axillary granulomas seen since: (1) large quantities of sodium stearate are required to produuce the granulomatous response, (2) stearate granulomas resolve within a few weeks, (3) stearate will elicit granulomas regularly in every individual, and (4) patients with clinical deodorant granulomas show the normal response to stearate. However, the most spectacular distinction between the allergic and non-allergic granulomas relates to the quantity which one must inject in order to produce the two responses. In the zirconium granuloma, it is necessary to inject only a fraction of a microgram. With the stearate, in order to produce a comparable but non-allergic lesion, there must be a thousandfold increase in the quantity introduced.

The zirconium deodorant granuloma is a prototype of the allergic granulomas seen in man. Histologically it is composed of nests of epithelioid cells, without central necrosis or caseation and with minimal associated inflammatory reaction. The development of this pattern and its immutability for months to years, once its peak has been reached, are outstanding features of this type of granuloma. There is no piecemeal destruction of a central mass of insoluble or particulate matter as is seen in various *foreign body granulomas*. There is no palisading of the epithelioid cells peripherally about a central caseous or necrotic mass with an outside rim of monocytes as is seen in the tuberculoid granulomas such as tuberculosis, syphilis, and mycotic infections. There is simply gradual growth and transformation of reticulo-endothelial cells into stable epithelioid cells apparently as a result of antigen-antibody reaction. This is a focal process at first, perivascular in the main, but ultimately the picture is quite diffuse with replacement of most or all of the normal tissue. This type of granulomatous patterning has been referred to as "epithelioid" or "sarcoid" and is seen classically in such conditions as sarcoidosis and tuberculoid leprosy. It is not possible at this time to state that these diseases, which resemble the allergic zirconium deodorant granuloma histologically, are necessarily totally allergic in nature themselves. However, with the knowledge that a simple chemical, zirconium, can of itself produce the diffuse, sarcoid-type granuloma as described herein, we should critically evaluate these and other granulomatous diseases with this possibility in mind. There is some evidence to indicate that both sarcoidosis and tuberculoid leprosy do represent allergic granulomas

in the strict sense. Support for such a view is found in the Kveim test, in which the intradermal injection of a 10% saline suspension of sarcoid tissue produces a granulomatous papule at three to five weeks in most cases of sarcoidosis. The allergen or granulomagenic material in the Kveim antigen has not yet been identified. Similarly, intradermal inoculation of a phenolized, ground-up suspension of lepra bacilli will produce, in patients with tuberculoid leprosy (but not in those with lepromatous leprosy), a granulomatous papule at three weeks. This reaction, known as the Mitsuda reaction, is an aid in the diagnosis of tuberculoid leprosy and indicates a hypersensitivity of these patients to some fraction of the mycobacteria. Beryllium and silicon granulomas also may represent allergic granulomas and should be investigated from this standpoint. Intradermal testing with dilutions of beryllium or silicon salts might well indicate that these patients have a hypersensitivity to these metals which could be responsible for their granulomas.

It is not necessary to postulate an allergic mechanism to explain the pathogenesis of foreign body granulomas since the process seems to be simply one of phagocytosis of the foreign material by the reticulo-endothelial cells. Extensive discussion of the possible importance of an allergic process in the development of the tuberculoid granulomas is not within the scope of this paper. Patients with tuberculosis, deep fungous infections, syphilis, do have an associated allergic hypersensitivity, as indicated by a tuberculin-type (48 hours) response to skin test antigen preparations of the various organisms. However, this allergic response is *not* granulomatous in nature and, unlike the Kveim or Mitsuda reactions, does not necessarily indicate that a granulomatous stage of the disease is present. As exemplified by the Mantoux tuberculin test, a positive skin test merely indicates previous exposure and sensitization (with the tuberculin-type allergy) to the purified protein derivative of the tubercle bacillus. The pathogenesis of the tuberculoid granulomas does not seem to have been satisfactorily explained on the basis of secondary reaction to the organisms themselves, their products, or as a result of tissue destruction[30]. Its elucidation awaits further study.

Summary

A new dermatologic entity, the zirconium deodorant granuloma, has been described and experimental and clinical studies regarding its pathogenesis reviewed. It has been shown that the zirconium deodorant granuloma is the result of an allergic hyperesensitivity on the part of the affected individuals to the metal, zirconium, which manifests itself as a granuloma. This, to our knowledge, is the first demonstration in man, that an allergic processs can be responsible for the development of a granuloma. The significance of this new form of allergy in relation to other granulomatous disorders in medicine is discussed.

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RECENT ADVANCES IN BLOOD COAGULATION WITH REGARD TO ANTICOAGULANT THERAPY, FIBRINOGEN, HEMOPHILA AND PLATELET DISORDERS*

SHIRLEY A. JOHNSON, Ph.D.**

Studies in blood coagulation which have been pursued for many decades in clinical entities such as hemophilia have suddenly become important in laboratory medicine because of the use of the oral anticoagulants. The problem of intravenous clotting is not well understood and a great deal of attention is being given to it. Since it is not known what elements in blood render it hypercoagulable, one therapeutic approach is to render the blood less coagulable by the administration of oral anticoagulants. Prothrombin time is prolonged when any coumarin or phenindione drug is given.

The prothrombin time (Table I) is a general test involving the addition of tissue

TABLE I

PROTHROMBIN TIME	
PLASMA, OXALATED	0.1 ML.
$CACL_2$	0.1 ML.
TISSUE THROMBOPLASTIN	0.1 ML.
CLOT APPEARS IN 14 SECONDS	

thromboplastin and calcium to plasma and observing the time that the plasma takes to form a clot. If excess or normal amounts of prothrombin and accelerators are present a short prothrombin time of approximately 14 seconds results. Our concepts of coagulation are shown simply in Table II. The prothrombin time measures the components involved in the activation of prothrombin in the presence of tissue thromboplastin. The right side of the Table represents the activation of prothrombin without tissue thromboplastin but with platelets and the various co-factors of platelets which are normally found in plasma. Tissue thromboplastin is not normally present in the circulating blood and is thought to be released only from the surrounding tissue by a break in the surface of the blood vessel caused by trauma. The oral anticoagulants reduce prothrombin and autoprothrombin I, both of which affect the prothrombin time by prolonging it, and autoprothrombin II. Autoprothrombin II is involved in one of the hemophilias and its concentration does not affect the prothrombin time.

It is possible that the oral anticoagulants reduce or alter some other factor which has not yet been identified and that this unidentified component moves parallel to the two factors, prothrombin and autoprothrombin I, which do affect the prothrombin

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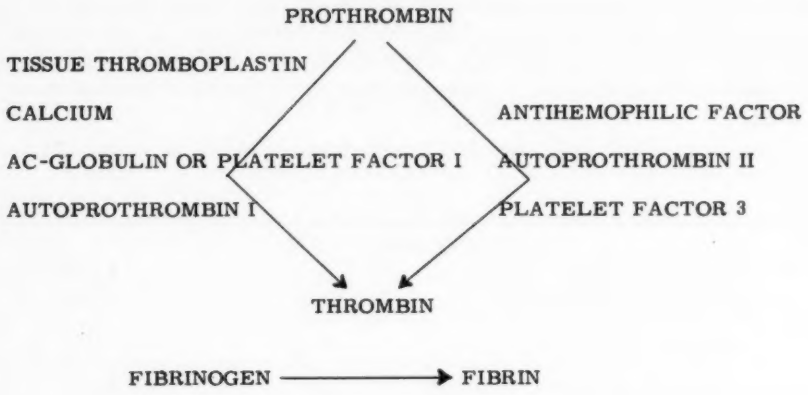
time. This unidentified component may be the more important factor in the prevention of thrombosis. It is known that the prothrombin time gives an accurate gauge of the dosage of the oral anticoagulant, and for this reason it is an important test in blood coagulation.

Table II shows that a small quantity of thrombin, just a fraction of a unit, will greatly shorten the prothrombin time by converting the fibrinogen to fibrin and eliminating the prothrombin to thrombin step. If enough anticoagulant has been given

TABLE II



CONCEPT OF COAGULATION

to prolong a 14 second prothrombin time to 30 seconds, a little thrombin can shorten this to 17. A physician may note a 17 second prothrombin time, expect 30 and increase the dose of anticoagulant. The next day instead of 30 seconds as expected he finds 45. The small amount of thrombin should be kept out of the blood in the first place. The blood is mixed in the tube with sodium oxalate immediately after it is drawn. The tissue thromboplastin in the form of tissue juices initiates the coagulation processes and that small amount of prothrombin is converted to thrombin and the cycle begins. Contrary to popular belief the prothrombin time of a specimen of plasma is constant throughout a day. Prothrombin and the accelerators involved in the activation of prothrombin are fairly stable for eight hours or so at room temperature. What this means is that a prothrombin time is rarely falsely prolonged, but only falsely shortened.

Except in the laboratory measurement of dosage of anticoagulant, the field of blood coagulation has contributed little to the management and understanding of thrombosis. The most important aspect of blood coagulation in the clinical sphere in the five next years will be, no doubt, in the area of clot dissolving or fibrinolysim. While the method of preventing the formation of the clot is not yet available, it does appear that more is known about how to dissolve the clot once it has formed. Within the next five years an intravenous fibrinolysim will probably be developed for thrombophlebitis, intravascular thrombosis and even coronary thrombosis. The problem is that

normal blood contains a profibrinolysin in an inactive form and how it is activated to active fibrinolysim has never been discovered. (Table III) It may be an activator which is called urokinase because it is found in urine. Whether or not this is the actual in vivo method is not yet known for certain. Streptokinase is another activator of fibronolyism but is not the natural one.

TABLE III

PROFIBRINOLYSIN

ACTIVATORS

UROKINASE

STREPTOKINASE

TISSUE ACTIVATOR

UNKNOWN SOURCE

↓

FIBRINOLYSIN

FIBRIN ⟶ DISSOLVED CLOT

POSSIBLE ACTIVATORS OF PROFIBRINOLYSIN

In addition to finding the best and, if possible, the natural activator of profibrinolysin, another problem exists. Some investigators believe that once the clot has formed from the whole blood and sufficient profibrinolysin is incorporated into the clot, lysis will take place if activator alone is added so only one of the experimental intravenous preparations contains activator. Another intravenous preparation contains excess activator, as well as some profibinolysin, and, of course, the various activators vary. One of the most exciting races in the pharmaceutical industry is in this field. While intravenous clot prevention is probably a long way off, lysis of the intravenous clot is near at hand.

The two aspects of blood coagulation so far discussed, namely, anticoagulant dosage control and administration of fibrinolysin are recent. Hemophilia, which has been known for centuries, is the time honored problem in blood coagulation. Prior to World War II there was some debate about whether hemophiliacs bled due to a defect in their platelets or to a plasma defect. Brinkhous[1] showed that the hemophilic platelets were normal when removed from normal blood but that the plasma recalcification time was long. The prothrombin time is normal. This is easy to understand with reference to Table II. The antihemophilic factor acts with platelets to activate prothrombin in a somewhat slower fashion than tissue thromboplastin but in a rather analagous way. Therefore formation of activity between platelets and the antihemo-

philic factor is called blood thromboplastin and can be measured by the thromboplastin generation test. The formation of blood thromboplastin requires neither extravascular materials nor a break in the lining of the vessel. For these reasons, tissue thromboplastin added to the plasma will mask this formation of blood thromboplastin, and normal and hemophilic plasma will give a normal prothrombin time. (Table IV)

TABLE IV

LABORATORY TESTS IN HEMOPHILIA

PROTHROMBIN TIME	NORMAL
PLASMA CLOTTING TIME (RECALCIFICATION TIME)	PROLONGED
CLOTTING TIME	PROLONGED
PROTHROMBIN CONSUMPTION TIME	ABNORMALLY SHORT

Classical hemophilia is concerned with a deficiency in the antihemophilic activity but the kind of defect is not agreed upon by investigators in this field. A controversy exists between those who believe that it represents the actual lack of a factor and those who believe that the antihemophilic factor is present but its activity is masked by association with an inhibitor. For practical purposes it does not matter as treatment would be the same regardless of the mechanism of the defect. The antihemophilic factor is unstable in whole blood or plasma. Perhaps it becomes conjugated with its inhibitor unstable in whole blood or plasma. Perhaps it becomes conjugated with its inhibitor as it does when blood clots for there is no antihemophilic activity in serum. Treatment of a hemophiliac is one of the rare instances in which fresh blood should be given. Many investigators recommend giving a bleeding hemophiliac blood which is less than 12 hours old.

The above remarks pertain to classical hemophilia. In 1952 independently in California and in England another kind of hemophilia was described. The term hemophilia has been enlarged to include any defect in the plasma factors which act with platelets. There are now considered to be at least two factors and some investigators believe there are more. Aggeler and associates[2] called their deficient factor plasma thromboplastin component and the disease PTC. Biggs and associates[3] named it Christmas disease from the name of their patient. (Table V)

Whether the PTC factor or Christmas factor acts with the antihemophilic factor together with platelets or whether one acts with platelets to form a product which then acts with the other is not known. But the two components, the antihemophilic factor and PTC, do act with platelets in some rather complicated fashion. Hemophilia is a rare disaese. Most clinical bleeding problems are concerned with platelet disturbances. However, there are those who feel that platelets have no relation to coagulation.

The thrombocytopenias, primary or secondary, comprise the largest group of bleeding problems. From an investigative point of view the coagulation of blood without platelets is a fascinating concept. It is considered that a platelet count of 50,000 or less will cause bleeding and yet the whole blood clotting time or Lee White

TABLE V
TYPES OF HEMOPHILIA

NAME OF DISEASE	FACTOR INVOLVED
CLASSICAL HEMOPHILIA	ANTIHEMOPHILIC FACTOR
PTC DEFICIENCY OR CHRISTMAS DISEASE	PTC OR CHRISTMAS FACTOR
PTA DEFICIENCY	PTA?

of such blood is normal. Blood will clot in the thrombocytopenic state but it clots differently when an abundance of platelets is available. Blood clots differently when platelets are reduced as evidenced by the fact that the prothrombin consumption time is greatly shortened in thrombocytopenic serum.

The prothrombin consumption time is based on the Quick prothrombin time, the difference being that the prothrombin consumption time is carried out on serum. In normal serum the prothrombin is reduced from about 250 units per millilitre to about 20 units and some accelerators of prothrombin activation are formed as blood clots. If prothrombin time is carried out on normal serum, that is the addition of thromboplastin and fibrinogen, instead of a value of 14 seconds one of 30 or more is found. So the normal prothrombin consumption time is prolonged and if the coagulation is incomplete and residual prothrombin remains in the serum the prothrombin consumption time is shortened. The prothrombin time is easily carried out if the serum is carefully defined such as whole blood that has been permitted to clot for one hour at a standard temperature. The end products of coagulation differ considerably depending on the time that serum is examined. The thrombin, which forms when blood clots, disappears due to the action of antithrombin. As a result, serum 30 minutes old contains thrombin which is almost completely absent in serum 60 minutes old.

If platelets are reduced to the thrombocytopenic state the prothrombin consumption time on such blood is shortened abnormally. However, there is little or no residual prothrombin in the serum. The short prothrombin consumption is due to the formation in abnormal amounts of an accelerator when blood clots. It is probable that this accelerator is a derivative of prothrombin because chemically it resembles prothrombin. From an investigative point of view the mechanism of action of blood coagulation in the thrombocytopenic state is an intensely interesting one. However, at the moment the therapeutic problem must be approached from the other end, that is, replacement of platelets.

Platelet transfusions and platelet substitutes are used in various parts of the country. Whole fresh human platelets are the logical source but economically this presents problems. However, most platelets in bank blood are lost because the platelets have disintegrated before the blood is transfused. It is feasible to collect the platelets from each pint of blood as the blood comes into the blood bank and to lyophilize the platelets and store them till needed. The most active factor in platelets, platelet factor 3 or the thromboplastic factor of platelets, is destroyed with lyophilization which is a disadvantage of this method. Huge quantities of platelets are required to control

bleeding. An attempt to use a purified platelet factor 3 preparation from bovine sources in secondary thrombocytopenia has been made at the Henry Ford Hospital with some success.[4] There have been no antigenic problems, perhaps because the reticulo-endothelial system is damaged in these patients. This bovine platelet preparation is sterilized using beta-propriolactone and ultraviolet radiation.[5] However, as yet the best platelet substitute has not been worked out.

Another aspect of platelet work is concerned with a group of fifteen patients who bleed because of defective platelets.[6] The condition is designated as thrombocytopathy. This group of fifteen patients had mild bleeding manifestation, and most laboratory findings were normal except the bleeding time which was over 20 minutes and the prothrombin consumption time which was 14 seconds. This suggested a platelet dysfunction and the platelets were collected from 100 ml. of blood and assayed in the thromboplastin generation test. It was found that a suspension of equal numbers of normal platelets generated more thromboplastic activity than those of the patients. There are many platelet factors but we feel that the one most responsible for activation of prothrombin and generation of blood thromboplastin is probably platelet factor 3. This platelet activity is also specific for platelets. There is no comparable activity in plasma. Using a specific platelet factor 3 assay involving the activation of purified prothrombin in the presence of the antihemophilic activity the platelets from these patients activated less than one hundred units of prothrombin to thrombin while platelets activated 800 units per millitre.

Rebuck and associates[7] studied these platelets morphologically using the phase and electron microscopes. It is considered that platelets pass through four stages in the process of disintegration. The round or circulating type which is opaque to electrons is believed to become the dendritic form. The dedritic form changes into the intermediate form and then to the less dense spread type. Electron micrographs of normal blood show most of the platelets in the dendritic stage. The platelets of these patients, however, are mostly in the spread stage. A platelet count of the blood of seven of the patients was carried out under the electron miscroscope and revealed about 26 per cent of their platelets to be in the dendritic stage, compared to 80 per cent of the platelets in normal blood. It is possible that this represented a kind of platelet that did not rupture easily and so could account for the pile-up at this later stage. This would mean that the platelets of these patients had adequate amounts of platelet factor 3 but could not release it. This was tested by disintegrating the platelets in a sonic oscillator and measuring the platelet factor 3 activity. The activity of these patients' platelets has increased from the ability to activate 200 units per millilitre of purified prothrombin to thrombin to 600 units per millilitre, when they are thoroughly disintegrated. We feel that we have elucidated, in part, the fault in these platelets but what the satisfactory therapeutic measure will be is another problem.

Another aspect of platelet dysfunction has been found in uremia. Some uremics bleed. The laboratory tests in coagulation appear to be normal except that the prothrombin consumption test in some cases is abnormally short. Like the thrombocytopenic state and thrombocytopathy this short prothrombin consumption was not due to residual prothrombin but probably due to the formation of an accelerator. Platelets from the uremic patients are obtained by differential centrifugation from

100 ml. whole blood, washed in saline three times, and then resuspended in saline at a known concentration per cu.mm. These fresh whole platelets were used to determine clot retraction by the method suggested by Hartman and Conley.[8] The uremic plasma and platelets were compared with that of normal and found to have normal retraction.

Platelet factor 3 assays were carried out and found to be markedly decreased. Previous studies on thrombocytopathy A showed that platelets deficient in factor 3 would give normal activity after being fragmented by sonic treatment. This procedure was carried out on the uremic platelets, but no increase in activity was obtained. This suggests that the defect in uremia is different from that in thrombocytopathy A. It has been postulated that in thrombocytopathy A the platelet factor 3 activity is present in normal amounts; however, the platelets do not disintegrate normally to release it. But in the uremic condition the platelets appear to be actually deficient in the activity. Preliminary studies done by electron microscopy have shown the uremic platelets to be normal morphologically.[9] A considerable study on morphology of thrombocytopathy A platelets have shown them to be abnormal morphologically. Possibly this difference in morphology is closely related to the difference in the activity obtained in thrombocytopathy A after sonic treatment and the lack of activity obtained from uremic patients' platelets.

Thromboplastin generation tests were done using platelets harvested from uremic platelets and these were found to generate far less thromboplastin than platelets from normal individuals. Since many metabolites in the blood are altered in uremia, the possibility arises that they could be responsible for the destruction of platelet activity. To test this possibility, normal platelets were suspended in uremic plasma and incubated at 8° C for 18 hours. Then the platelets were centrifuged and washed and their activity tested. The platelet factor 3 activity of this platelet extract was greatly decreased. The thromboplastin generation test was also done and it was found the platelets which had been incubated in uremic plasma did not generate as much thromboplastin as those incubated in normal plasma. It is too early in this investigation to be able to draw any definite conclusions, but the cause of the loss of platelet factor 3 activity will probably be closely associated with the metabolites of uremia.

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